Review Article

Apremilast in Psoriasis and Beyond: Big Hopes on a Small Molecule

Abstract

Apremilast, an orally administered small molecule inhibitor of phosphodiesterase 4 (PDE4), has been licensed by the US Food and Drug Administration for the management of active psoriatic arthritis (March 21, 2014) and moderate to severe plaque psoriasis (September 23, 2014). It has got approval from Drug Controller General of India for marketing in India in 2017. The drug has drawn much attention from the practising dermatologists for its commendable safety profile and prescription convenience. Introduced initially as an orally administered small molecule in psoriasis patients, the drug has now been used in various other indications as evident by the recent surge in literature for its off-label uses. 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.

Keywords: *Apremilast, efficacy, psoriasis, psoriatic arthritis, safety, small molecules*

T. P. Afra, Muhammed Razmi T, Sunil Dogra[1]

Department of Dermatology, IQRAA International Hospital and Research Centre, Calicut, Kerala, [1]Department of Dermatology, Venereology, and Leprology, Postgraduate Institute of Medical Education and Research, Chandigarh, India

Psoriasis is a chronic inflammatory dermatosis with a waxing and waning course. The management of psoriasis has witnessed a tremendous change over the last 1 decade paving ways to the newer biological agents. While the common systemic agents, such as methotrexate, acitretin, and cyclosporine are associated with end-organ toxicities and treatment-related side effects, the biological agents have the limitations of added costs to the care and inconvenient mode of administration apart from the possibility of iatrogenic immunosuppression. In this background, an agent that is less toxic, cost-effective, convenient to prescribe, and having optimal efficacy is always welcomed by the patients and dermatologists. Apremilast (Otezla; Celgene) was approved by the US Food and Drug Administration (FDA) on March 21, 2014, for the management of active psoriatic arthritis (PsA) in adults. Soon, on September 23, 2014, FDA approved apremilast for treating patients of moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy.[1] It has got marketing approval from Drug Controller General of India in 2017. However, there is a paucity of information on apremilast in the Indian literature. Moreover, the existing literature is more focused on its usefulness in PsA. In this review, we would like to comprehensively yet concisely discuss the various clinical aspects of apremilast use in psoriasis and PsA and briefly narrate experience of its use in various inflammatory dermatoses.

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. Salient differences between small molecules and biological agents have been highlighted in Table 1.

Recently, there is a surge in newer small molecules being licensed for dermatological conditions and also the preexisting small molecules are being explored for newer indications [Table 2]. Of these, apremilast has gained major attention from the practising dermatologists for its versatile

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Address for correspondence:
Dr. Sunil Dogra, Department of Dermatology, Venereology and Leprology, Postgraduate Institute of Medical Education and Research, Sector 12, Chandigarh - 160 012, India. E-mail: sundogra@hotmail.com

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use in psoriasis and other inflammatory skin conditions. A thorough knowledge about this drug may benefit the clinicians to tailor their treatment regimen for optimizing the efficacy and tolerability.

Pharmacology

Phosphodiesterase (PDE) 4 has a role in immune regulation by degrading cyclic adenosine monophosphate (cAMP), a key second messenger. Apremilast suppresses intracellular PDE-4 causing accumulation of cAMP within the cell which modifies the downstream signalling pathways in cells of the innate (e.g., monocytes) and adaptive (e.g., T cells) immune system and nonimmune cells (e.g., keratinocytes, synovial fibroblasts). As a result of PDE-4 inhibition, the levels of proinflammatory cytokines like tumor necrosis factor alpha (TNF-α) and interleukin (IL)-23 decrease and those of anti-inflammatory mediators like IL-10 increase.[2]

Table 1: Salient differences between small molecules and biological agents

Parameter	Small molecules	Biologics
Molecular weight	Small <1000 Da	Large >1000 Da
Chemical composition	Organic small molecule	Protein
Target specificity	Intracellular-less specific	Extracellular-more specific
Mechanism of action	Enzyme inhibition	Blocking/depletion
Half-life	Usually short	Longer
Stability	Usually stable	Heat and protease sensitive
Distribution	Potential for extensive distribution	More limited distribution
Administration	Oral/topical	Parenteral
Immunogenicity	Generally not a concern	Common concern
Manufacturing cost	Low/variable	High

The absolute bioavailability of apremilast is around 73%. Its concentration in the plasma peaks (Cmax) in a median of around 2.5 hours; food intake does not affect its clinical activity. Apremilast is metabolized extensively by both CYP-mediated (mainly CYP3A4) oxidative mechanisms (followed by glucuronidation) as well as non-CYP mediated hydrolysis.[3] Hence, serum levels and the efficacy may be decreased by coadministering with the potent CYP enzyme activators like rifampicin, carbamazepine, phenytoin, and barbiturates.

Mild to moderate renal dysfunction or moderate to severe hepatic dysfunction do not change the pharmacokinetics of apremilast to a significant level clinically. However, dose reduction is recommended in those with severe renal dysfunction.[3]

Dosage and Formulations

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 [Table 3]. 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 psoriasis[4] has also been developed, though not yet available commercially.

Clinical Uses

Licensed uses of apremilast include management of moderate to severe plaque psoriasis and active PsA not

Table 2: Newer small molecules

Group	Molecule	Major indications
PDE-4 inhibitors	Apremilast	Psoriasis, psoriatic arthritis
	Crisaborole	Atopic dermatitis
	Roflumilast	Chronic obstructive pulmonary disease
	RVT-501	Atopic dermatitis
JAK-STAT inhibitors	Tofacitinib	Rheumatoid and psoriatic arthritis, ulcerative colitis.
	Ruxolitinib	Atopic dermatitis, alopecia areata, psoriasis, and vitiligo Myelofibrosis, polycythemia vera.
	Baricitinib	Atopic dermatitis, alopecia areata, psoriasis, and vitiligo Psoriasis
Protein kinase C inhibitors	Sotrastaurin	Prevention of transplant rejection, psoriasis
Tyrosine kinase Inhibitors	Masitinib	Amyotrophic lateral sclerosis
	CT327	Pruritus in psoriasis
MAPK inhibitors	BMS-582949	Atherosclerosis
Adenosine A3 receptor agonist	CF101	Rheumatoid arthritis, and psoriasis
Fumaric acid esters		Psoriasis

Table 3: Dose escalation schedule for apremilast

Day	AM	PM
1	10 mg	-
2	10 mg	10 mg
3	10 mg	20 mg
4	20 mg	20 mg
5	20 mg	30 mg
6	30 mg	30 mg

responding adequately to disease-modifying antirheumatic drugs (DMARDs). The drug has been extensively studied for these two indications. However, recently, it is tried for many other indications where there is a role for cAMP-mediated anti-inflammatory action [Table 4].

Psoriasis

The efficacy and safety of apremilast were established through well-conducted clinical trials which showed superior efficacy over placebo. Unlike the clinical trials that followed strict protocols in patient follow-up and treatment plan, the real world data have revealed even better efficacy with the achievement of Psoriasis Area and Severity Index (PASI)-75 in half of the studied population[5,6] (c.f one-third in ESTEEM trials). Apremilast was also found to improve psoriasis at difficult sites like palmoplantar, nails, and scalp. It also significantly improved the pruritus and patient quality of life. The outcome of various studies addressing its efficacy as monotherapy in psoriasis is outlined in Table 5. Evidence from various clinical studies has established the efficacy of apremilast monotherapy irrespective of previous exposure to the systemic agents.[5,7-9] However, in a matching-adjusted indirect comparison of data from pooled trials, efficacy of apremilast was found to be inferior to calcipotriol/betamethasone dipropionate (Cal/BD) [0.005%/0.05%] aerosol foam, (30.4% vs. 52.7%; $P < 0.001$). However, 4 weeks of Cal/BD foam has also shown superior efficacy over 12 weeks of methotrexate, or acitretin.[10]

Combination therapy [Table 6].: In a long-term study, efficacy and safety of single drug and multidrug treatment (methotrexate, etanercept, and ustekinumab) with apremilast in psoriasis was analyzed and was found that treatment response at 52 weeks was maintained in similar proportions of patients in both the groups (monotherapy, 66.7%; combination therapy, 63.0%; $P = 0.787$). Proportions of adverse effects were also comparable between the groups (single drug, 14.3%; multidrug, 22.2%; $P = 0.484$).[11] Safety was not compromised on combining apremilast with other biologic agents in the management of psoriasis and PsA.[12] A retrospective study by Mayba and Gooderham has reported a better drug survival of apremilast in their patients who were also on other systemic agents (16%),[13] compared to poor drug survival reported in apremilast monotherapy (49%[14], 65%[15]). Hence, combining other systemic agents with apremilast may increase the treatment adherence of patients; however, additional therapeutic benefits in terms of efficacy or tolerability is subject of further research.

Psoriatic Arthritis

The PALACE 1, 2, and 3 clinical trials assessed apremilast in PsA patients who had previous treatment with conventional synthetic DMARDs (csDMARDs) and/or biologicals along with or without csDMARD.[16-18] PALACE 4 trial was done to analyze apremilast single-drug therapy in csDMARD and biological-naïve populations.[19] ACTIVE trial analyzed the effects of apremilast alone in patients of PsA who had no prior exposure to biologicals but had one csDMARD.[20] Apremilast (30 mg twice daily) use resulted in improvement of clinical features of psoriatic arthritis in both DMARD exposed and nonexposed patients. Around 30% in both the groups have achieved American College of Rheumatology (ACR) response criteria, ACR20 by week 16 compared to around 15% improvement with placebo. Health Assessment Questionnaire Disability Index score has also improved with apremilast compared to placebo. Regarding other indices like ACR50 or ACR70, no significant differences between apremilast vs. placebo group were noted in PALACE trials except in PALACE1 (ACR50 and ACR70) and PALACE4 (ACR50).[16-19] The ACTIVE trial has demonstrated early onset of action (at week 2) and sustained efficacy of apremilast at 52 weeks in biological-naïve patients with PsA.[20] Enthesitis, dactylitis, physical function, and fatigue were also improved in these trials, and a long-term sustained efficacy was also noted. A recent analysis of the pooled data from PALACE 1-3 trials has demonstrated efficacy of apremilast in improving enthesitis and dactylitis up to 3 years.[21] In a real world study, Ceccarelli *et al.* have ultrasonographically documented a prompt improvement (within 45 days) in joint inflammatory status with apremilast.[22]

Adverse Effects and their Management

Even though apremilast is a well-tolerated drug with a favourable safety profile, its use can cause some adverse events which can be troublesome to the patients leading to noncompliance and withdrawal from the treatment if not addressed timely. The adverse events reported most commonly (≥5% of patients) at its recommended dose in the clinical trials (ESTEEM 1 and 2, PALACE, LIBERATE, ACTIVE, Ohtsuki *et al*.) as well as real-world postmarketing surveillance were diarrhea, headache, nausea, nasopharyngitis, and upper respiratory tract infections.[8,17,20,23-25] The rates of these adverse events were more during the initial stages of therapy and most of them self-resolved over time. Other less common side effects were depression, suicidal tendency, and weight loss. Adverse events were found to be less common in real-world patients in comparison to clinical trials.[26] Although the product monograph warns against depression,

Table 4: Off-label dermatological indications of apremilast

Disease	Evidence	Outcome
Atopic dermatitis	Clinical trial[27]	A significant reduction from baseline of pruritus, DLQI and EASI
	Case series[28]	Improvement in erythema, scaling, and xerosis of lesions as well as pruritus with a standard dose of apremilast in five adults
	Case report[29]	Quick and long-lasting relief of intense pruritus with half the standard adult dose in an 8-year-old boy with moderate to severe atopic dermatitis
Alopecia areata (AA)	RCT[30]	No significant improvement from baseline in patients with >50% scalp involvement. $SALT_{50}$ has been achieved only in 1/12 patients in apremilast group
	Case series[31]	No improvement in patients with severe alopecia areata
	Case Report[32]	Considerable hair growth in a patient alopecia universalis
	Animal study[33]	Apremilast prevented the onset of AA in a humanized mouse model
Aphthous stomatitis	Case report[34]	Rapid and substantial response of recalcitrant aphthous lesions
Behcet's syndrome	RCT[35] (Phase 2)	Apremilast effective in reducing the number and pain of oral ulcers, a higher rate of complete remission of oral ulcers
Cicatricial ectropion secondary to severe lamellar ichthyosis	Case report[36]	Use of apremilast for the concomitant plaque psoriasis resulted in optimal control of both his skin diseases and minimized the recurrence of eyelid ectropion
Epidermolysis bullosa simplex generalized (severe)	Multi-center prospective study[37]	Treated adults showed a marked decrease in the number of blisters
Recurrent erythema multiforme	Case series[38]	Complete clearance of the lesions was observed in all three patients with oral erythema multiforme including those refractory to other standard therapies
Hidradenitis suppurativa (moderate to severe)	RCT[39]	Hidradenitis Suppurativa Clinical Response was met in 8/15 (53.3%) in apremilast group compared to none out of five patients in placebo group, (P=0.055)
	Case series[40]	Significant improvements of the clinical score (Sartorius score), pain and HR-QoL (DLQI) with apremilast
Lichen planus (moderate to severe)	Case series[41]	Clinical improvement in all the case with 3/10 cases achieving the primary endpoint of 2-grade improvement
Palmoplantar pustulosis	Case series[42]	Three patients had near complete symptom resolution after 2 weeks on apremilast.
	Case report[43]	Symptom resolution within 4 weeks
Pyoderma gangrenosum (recalcitrant)	Case report[44]	Addition of apremilast to systemic steroid and methotrexate resulted in healing of erosions
Pityriasis rubra pilaris (refractory)	Case reports[45,46]	Significant improvement in erythema, keratoderma and nails
Generalized pustular psoriasis (GPP)	Case report[47]	Complete clearance of plaque psoriasis and GPP
Inflammatory rosacea	Open-label pilot study[48]	Significant reduction in erythema, but not in the number of papules and pustules
SAPHO syndrome	Case report[49]	Achieved long-lasting disease control
Hailey-Hailey disease	Case series[50]	Moderate improvement in the lesions. Two patients had relapsed fter the study period of 60-10 months
Chronic cutaneous sarcoidosis	Case series[51]	Significant improvement in the induration with no change in erythema, desquamation or area of involvement at week 12. Relapse noted in 3/15 patients on treatment cessation
Vitiligo	Case report[52]	Repigmentation of refractory lesions noted with apremilast in conjunction with systemic steroids, in a patient who was previously not responding to multiple systemic agents including systemic steroids
Antilaminin gamma-1 pemphigoid associated with psoriasis	Case report[53]	Improvement in blisters along with psoriatic lesions on apremilast in conjunction with systemic steroids

RCT=Randomized controlled trial

its incidence was not shown to increase in long-term safety analysis.[23] Weight loss was noticed more in patients with higher baseline body mass index and in the first year of treatment and did not result in any clinical sequelae.[23] Serious adverse events reported rarely were major adverse cardiac events, chronic obstructive pulmonary disease, renal calculi, and urinary tract infection.[54] Rare side effects include diverticulitis, hyperpigmentation, postinflammatory lentiginosis, purpura annularis telangiectodes of Majocchi, persistent epiphora, and fanconi syndrome.[55-60] Apremilast is an anti-inflammatory drug and does not cause immunosuppression. Laboratory parameters also did not

Table 5: Clinical studies on the use of apremilast in psoriasis

Study	Treatment (mg BD)	Subjects	Baseline severity (SD)	End point (follow-up)	Efficacy (%)	≥1 adverse events with Ap	Remarks
North-American study[61]	Ap 10 vs. Ap 20 vsAp 30 vs Pl	89 vs. 87 vs. 88 vs. 88	PASI: 18.5 (6.6); BSA(%):22.0 (12.7)	16 w (24 w)	PASI-75: 11% vs. 29%* vs. 41%* vs. 6%	75.0%	Phase 2b trial Most (>96%) AEs were not severe
Japanese bridging study, Ohtsuki *et al*.[24]	Ap 20 vs. Ap 30 vs. Pl	85 vs. 85 vs. 84	PASI: 21.2; BSA (%): 30.3	16 w (68 w)	PASI-75: 23.5%* vs. 28.2%* vs. 7.1%	51.8%	Phase 2b trial Efficacy maintained and the AEs did not increase with continued apremilast treatment (up to 68 weeks)
ESTEEM 1	Ap 30 vs. Pl	562 vs. 282	PASI: 18.7 BSA(%): 24.4	16 w (52 w)	PASI-75-33.1* vs. 5.3	69.3%	Phase 3 trials.[7,27] Significant improvement in nail, scalp and palmoplantar psoriasis Improvement in QoL and pruritus indices also
ESTEEM 2	Ap 30 vs. Pl	274 vs. 137	PASI: 18.9 BSA (%): 25.5	16 w (52 w)	PASI-75-28.8* vs. 5.8	68.0%	
LIBERATE[8]	Ap 30 vs. Et 50 vs. Pl	83 vs. 83 vs. 84	PASI: 19-20 BSA: 27-28	16 w (52 w)	PASI-75-40%* a vs. 48%* vs. 12%	71.1%	Phase 3 trial PASI-75 was 53% in patients who got Ap throughout the study and those who switched from Pl to Ap at week 16. It was 56% in those who switched from Et to Ap
Mayba *et al*.[13]	Ap	81	BSA: 9.6% PASI: 10.4 DLQI: 13.7	39 w	BSA <1: 37%	61.7%	Retrospective study
Wong *et al*.[6]	Ap	59	PASI: 16.1 DLQI: 16	16 w	PASI-75: 47% PASI-90-100: 25% DLQI: 7	45.8%	Prospective case series
Armstrong *et al*.[9]	Ap in systemic naïve and systemic experienced patients	7517	PGA: 2.8 & 2.5 BSA: 17.8 & 12.9 Itch NRS: 4.1 & 3.8	24 w	PGA reduction: 1.7 and 1.0 PGA 0-1: 26.8% & 25.5 BSA reduction: 62% & 60% Itch NRS reduction: 2.4 & 0	NA	Retrospective, multicenter, longitudinal, observational cohort study. Higher patient satisfaction on patient-perceived overall treatment effectiveness
Vujic *et al*.[62]	Ap	48	PASI: 10.7	12.5 w	PASI-75: 18.8% PASI-90: 6.3%	64.6%	Prospective real world data Patient weight inversely correlated with a PASI50 response
Papadavid *et al*.[5]	Ap	51	PASI: 10.8 DLQI: 11.1 PGA: 2.7	16 w	PASI: 4.3 DLQI: 3.9 PGA: 1.3 PASI-75: 59.3% PASI-100: 17.9%	30.0%	Prospective case series Most of the patients (84%) had prior exposure to systemic therapy, signifying a difficult to treat psoriasis group

Contd...

Table 5: Contd...

Study	Treatment (mg BD)	Subjects	Baseline severity (SD)	End point (follow-up)	Efficacy (%)	≥1 adverse events with Ap	Remarks
Knuckles *et al*.[63]	Ap	70	BSA: 9.9%	24 w	BSA: 4.9%	12%	Prospective chart review and online survey Most (68%) dermatologists expressed that Ap met their expectations
Ohata *et al*.[64]	Ap±other systemic agents including biologics	50	PASI: 10.1	26 w	PASI: 5.3	76.0%	Real world data from Japan 33.3% have achieved PASI75/90. Drug survival was 70%. Higher occurrence of diarrhoea (60%) compared to western data
Kishimoto *et al*.[65]	Ap±other systemic agents including biologics	44	-	25 w	PASI-100: 11.4%	55.6%	Small plaques responded to Ap better than large plaques

*Significant at ^{p}<0.05. a - Not significant between apremilast vs. etanercept. AE=Adverse event; Ap=Apremilast; Et=Etanercept; Pl=Placebo; NA=Not available

Table 6: Studies on combination therapy with apremilast

Combinations used	Evidence	Outcome
Methotrexate, etanercept, and ustekinumab	Multicenter, retrospectivereview[11]	Comparable long-term (52-week) efficacy and safety with monotherapy and combination therapy
NB-UVB, methotrexate, cyclosporine, acitretin, TNF inhibitors, ustekinumab	Retrospective chart review[66]	Apremilast is a relatively safe and effective treatment in combination with systemic, biologic, or phototherapy in the treatment of inadequately controlled chronic plaque psoriasis
NB-UVB	Open-label study[67]	A high treatment response (PASI 75 in 73% at week 12) without any unexpected safety signals in patients with moderate to severe plaque psoriasis
Adalimumab	Case report[68]	Plaque type psoriasis recalcitrant to topical, oral, and biologic mediations attained almost complete remission
DMARDs	PALACE1 RCT (phase 3)[69]	Apremilast efficacious in psoriatic arthritis regardless of concomitant DMARD use
Secukinumab	Case report[70]	Significant skin improvement with minimal drug side effects in recalcitrant plaque psoriasis and psoriatic arthritis
Infliximab	Case report[71]	Maintenance of remission in generalised pustular psoriasis and acrodermatitis continua of Hallopeau after initial control with cyclosporine

RCT=Randomized controlled trial

show any clinically meaningful changes with apremilast treatment. Apremilast did not show any organ-specific or cumulative toxicity.[23] There was no increased risk of infections; opportunistic or reactivation of latent infections, induction of malignancy or other serious adverse events according to the studies on apremilast reported so far. Recurrence of melanoma was noted in a patient with a history of two previous melanomas with nodal metastasis after starting apremilast for psoriasis.[72]

Diarrhea

- It is the most common adverse event associated with apremilast treatment. Most cases are reported within the first 2 weeks of treatment and are self-resolving within 1 month even with ongoing apremilast.[8] It is of secretory type due to the activation of chloride channels on enterocytes resulting from increased cAMP[73]
- Supportive measures like maintenance of adequate hydration and avoidance of exacerbating factors like over satiety and bloating, dairy products, caffeine, and artificial sweeteners will control most of the episodes. Intractable diarrhea may necessitate pharmacological intervention with bulk-forming agents, bismuth subsalicylate, short-term loperamide, dose reduction, or even treatment discontinuation.[74]

Nausea

PDE inhibition at the chemoreceptor trigger zone and central neurokinin receptors causes nausea.[75] It is the most common AE, next to diarrhea. It can be managed adequately with supportive measures as

for diarrhea. Other treatment options include anticholinergic antihistamines (diphenhydramine, dimenhydrinate, promethazine), ondansetron, prochlorperazine, and amitryptilline.[74]

Headache

Recent real world data on apremilast report headache as one of the common adverse events.[26] Ensuring adequate hydration and sleep along with avoidance of stress and other trigger factors are firstline in the management of headache. Nonsteroidal anti- inflammatory drugs (NSAIDs) can be added if needed.[74]

Nasopharyngitis and Upper respiratory tract infections

Supportive measures like hydration, adequate sleep, avoidance of irritants, use of over the counter agents like nasal saline irrigation, antihistamines, and decongestants are useful in controlling upper respiratory tract symptoms. Antibiotics can be used in proven infections.[74]

Safety, Tolerability, and Drug Survival

Apremilast has been established as a safe and tolerable drug through various clinical trials and real-world studies. In a pooled safety analysis of two-phase 3 randomized controlled trials (RCTs, ESTEEM 1 and 2), adverse events resulted in the withdrawal of therapy only in 11.2% of patients.[23] In a retrospective study, though diarrhea was the adverse event recorded in a higher number of patients, the presence of a headache was the adverse event responsible for most of the apremilast discontinuation.[26] Although the adverse events were lesser in real-world settings (57.2% vs. 66.4%, $P < 0.05$), the proportion of adverse events leading to reduced tolerance and withdrawal was more (18.8% compared to 5.3%, $P < 0.001$) in comparison to clinical trials. It may be due to the more frequent clinic visits in clinical trials with possible attendance of patient queries which have resulted in increased tolerance and also the psoriasis being of the more refractory type in real-world patients. However, the studies on real-world patients are based on retrospective data and do not include active elicitation of adverse events.[25]

In a real-world retrospective study with endpoint at 16 weeks of apremilast treatment, 12% of study subjects discontinued the treatment during the initial 4 weeks due to adverse events (mostly gastrointestinal), and another 16% discontinued later owing to decreased efficacy.[5] In a recent systematic review and network meta-analysis of long-term PASI response of newer biologicals and small molecules, etanercept and apremilast were found to have a lowest expected efficacy.[76] In our personal experience, it was found that the patients respond to apremilast quite satisfactorily during the initial period. But, often we need to add other systemic agents or shifting back to the conventional agents after some time due to reduced efficacy. In this context, we would like to discuss some long-term drug survival studies on apremilast. Lee *et al.* have reported a failure rate of 49% after a median duration of 146 days of treatment.[14] In another study, a failure rate of 65% was noted after a median duration of 200 days.[15] Hence, it appears that around half of the patients discontinue apremilast treatment within 6–8 months due to various reasons including lack of efficacy.

Cost Analysis

To date, there are no direct comparative studies between apremilast or any other antipsoriatic medication. In an indirect comparative study on cost-effectiveness of apremilast over methotrexate, Armstrong *et al.*[77] have concluded that incremental cost per PASI-75 with apremilast was very high with no added benefit in terms of efficacy. The additional cost for apremilast over methotrexate for each PASI responder per year was $188,000, which would come around $160,000 if additional costs that would incur for the total monitoring and toxicity costs associated with methotrexate was included.[77] National Institute for Health and Care Excellence (NICE) has evaluated the clinical efficacy and cost efficacy of apremilast in two patient groups with moderate to severe plaque psoriasis (PASI >10 and a Dermatology Life Quality Index (DLQI) ≥10 vs. PASI <10 and a DLQI ≤10) as a part of its single technology appraisal process. In the first group with severe psoriasis, the company has claimed apremilast to be an additional line of management before starting biologicals and as a safe drug in the second group to whom the biological agents are not indicated at present. The evidence review group of this committee was highly critical of the company's claim on cost-effectiveness of the drug (e.g.,: a recently published study[78] funded by the company has shown a similar adherence and lower total healthcare costs with apremilast vs. biologic users), and concluded that the most probable incremental cost-effectiveness ratio for PASI >10 and a DLQI ≥10 group was about ≤30,300 per quality-adjusted-life-year (QALY), and this was higher than the threshold level normally regarded as cost-effective. The similar value for the second group (DLQI ≤10) would be double considering the otherwise less expenditure that would incur in this group with less severe disease.[79] In the context of PsA, according to NICE Appraisal Committee, cost savings obtained on addition of apremilast were not sufficient to make up for the lost clinical effectiveness as QALY was also decreased with apremilast.[80]

A recent systematic review on the cost-effectiveness of biologicals and small molecules in psoriasis concluded that adalimumab as the most cost-effective agent (100% of all aggregated pairwise comparisons), followed by ustekinumab (66.7%) and infliximab (60%). However, the same review has pointed to the conclusions of emerging literature favoring secukinumab (75%) and apremilast (60%).[81] Hence, further pharmacoeconomic

analysis regarding the cost-effectiveness of apremilast should be done in the context of superior efficacy reported with apremilast in the real world scenario in comparison to clinical trials.

Special population/situations

- Geriatrics (≥65 years of age): Geriatric population may have a more chance of developing common gastrointestinal complications with efficacy similar to as in younger adult patients. So, apremilast should be used cautiously in them. Geriatric patients comprised 10% and 9% of the total study population in PALACE and ESTEEM trials respectively and the efficacy and safety in them were similar to that in the younger population[82]
- Pediatric age group (<18 years of age): The safety and efficacy of apremilast in children have not been studied. Product monograph does not recommend its use in children. However, a case of atopic dermatitis in an 8-year-old boy successfully treated with apremilast (30 mg OD) has been reported.[29] Smith has reported successful use of oral apremilast as a monotherapy in a 14-year-old boy with chronic plaque psoriasis not responding well to topical therapy. Despite the use of adult dose (30 mg BD), no gastrointestinal or other side effects were reported.[83] Currently, a phase 2, multicenter, open-label trial is being conducted in children with psoriasis of age group 6–17 years[84]
- Pregnant Women: Apremilast is contraindicated during pregnancy and in women planning to conceive since it has not been studied in them.[85] FDA places it in pregnancy category C drugs. Direction should be given to stop apremilast at least 2 days before conception[86]
- Lactating Women: Animal studies have shown the presence of apremilast in breast milk. Hence, it is contraindicated in lactating females, considering the lack of human studies
- Renal Impairment: Dose modifications needed in those with severe renal impairment, (creatinine clearance of less than 30 mL per minute). During the initial dose titration, the evening dose is skipped and after 1 week, it is continued at 30 mg once daily dose[3]
- Hepatic Impairment: No dosage adjustment is needed
- Immunosuppression: Apremilast does not target any specific cytokine, but restores a balance of proinflammatory and anti-inflammatory milieu.[2] In a pooled safety analysis of apremilast in patients with psoriasis from two phase 3, RCTs (ESTEEM 1 and 2), there was no increased risk of opportunistic or latent infections like tuberculosis; even though the patients with history of tuberculosis were included in the study.[23] Apremilast was used successfully in a psoriatic patient infected with HIV and hepatitis C.[87] It has also improved psoriatic onychopathy in an HIV-infected patient with severe psoriasis[88]

  Since there are no adequate and well-controlled studies of apremilast in patients suffering from severe immunosuppression, severe acute infectious diseases and those on immunosuppressive medicines, an extra care is needed while using it in such subjects. The product monograph states that apremilast is not indicated in combination with potent immunosuppressants like biologicals and cyclosporine.[3] However, recent studies on combination treatments with apremilast did not find any serious adverse outcome with such a combination[66]
- Missed Dose: Take the next dose at theregular time without increasing the dose
- Overdosage: Immediate medical help should be sought and the patient should be managed symptomatically with supportive care.

Evaluation and Laboratory Monitoring

Body weight should be recorded prior to the initiation of treatment and monitored regularly. Extensive laboratory evaluation and monitoring prior to initiation or while on apremilast treatment is not needed as laboratory variables did not show any meaningful changes in the trials of apremilast.[23] However, pretreatment assessment of renal function is recommended and the dose of apremilast has to be modified in severe renal impairment. Apart from this, the S3 guidelines recommend evaluation of liver enzymes at baseline since there is no long-term experience on the use of apremilast in people with hepatic impairment.[89] Even though the apremilast product monograph does not recommend laboratory monitoring, the S3 guidelines recommend baseline and 3 monthly monitoring of complete hemogram, liver enzymes, and serum creatinine.

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 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.[90]

Position in the Treatment Landscape of Psoriasis: Recommendations and Practical Aspects

Recent S3 guidelines[89] on the management of psoriasis recommends apremilast as a second line option if the first-line systemic agents (methotrexate, acitretin, cyclosporine, fumaric acid esters, and phototherapy) fail, are contraindicated or are found to be intolerant. It is indicated for severe disease as defined by a PASI or DLQI score ≥10. NICE[91] recommends stopping apremilast if an adequate response is not attained by 16 weeks. An adequate

response is defined as attainment of PASI 75 or PASI 50 with a 5-point reduction in DLQI. Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) while strongly recommend csDMARDs and biological DMARDs (bDMARDs) in DMARD naïve patients with peripheral arthritis, recommend apremilast in this setting conditionally. GRAPPA guidelines also strongly recommend bDMARDs and apremilast in patients with peripheral arthritis with an inadequate response to csDMARDs. In patients with psoriatic arthritis and associated plaque psoriasis, GRAPPA strongly recommend csDMARDs, bDMARDs, and apremilast.[92]

Authors have observed a good safety profile with apremilast except for transient gastrointestinal discomfort and headache during the initial few weeks. Appropriate pretreatment counseling regarding the transient nature of these side effects and general measures to decrease gastrointestinal intolerance as discussed above (see adverse effects section) possibly assures compliance. A proactive approach of starting antacid and antiemetic during dose escalation itself may minimize nausea and vomiting symptoms in patients and increase the drug compliance and tolerability. In patients experiencing disturbing gastrointestinal side effects, dose escalation can be completed in 13 days instead of 6 days with single dose at night (off-label). However, in spite of all the measures, a small proportion of patients are unable to tolerate and continue apremilast in dose escalation phase itself. Authors have observed reasonable maintenance of efficacy with apremilast 30 mg once a day or 60 and 30 mg alternate days after their initial disease control in those adult patients who find difficult to tolerate 60 mg/day. It is a plausible treatment option for moderate to severe stable psoriasis (PASI 3-10) with relatively smaller thin plaques along with topical therapy. A recent study documented improvement in ultrasonic evidence of joint inflammation in PsA at half the recommended dose of apremilast.[22] Apremilast has a moderate efficacy in chronic plaque psoriasis, with improvement of lesions at special sites like scalp, palms, and soles. It may also have a pertinent therapeutic role in patients where palmoplantar eczemas and psoriasis are diagnostic dilemma. Though literature supports beneficial role of apremilast in nail psoriasis,[93,94] it needs to be substantiated in larger studies. Apremilast is a safe option for patients with immunosuppression as in those affected with HIV. It can be used in scenarios where other systemic agents are contraindicated or not desired as in hepatic impairment, cardiac diseases, metabolic diseases like diabetes mellitus, hypertension, or hyperlipidemia, doubtful posttreatment laboratory monitoring, etc. While biologic agents like etanercept or secukinumab may exacerbate or induce inflammatory bowel disease, apremilast is envisaged to decrease bowel inflammation.[95] Preliminary findings from an ongoing clinical trial report an improvement in ulcerative colitis symptoms and signs with apremilast.[96] Apremilast can be a better option than acitretin to use in women with childbearing potential since the contraceptive advice for a long duration is not necessary. It can also be used as a bridging or maintenance therapy after induction with a systemic agent like cyclosporine or methotrexate in individuals with frequent flares. In resource-poor settings, this low cost, moderately effective molecule with limited need of laboratory monitoring can be strategically used as an adjunctive or rotational therapy along with biologics and conventional systemic treatments for psoriasis minimizing the cost of treatment, side effects, and optimizing the outcome. In 2015, Otezla (apremilast, Celgene Corporation, USA) managed to earn revenues of about $471.7 million, the highest earned by any immunology and inflammation drug in the first full year of launch.[97] Full-year sales in 2017 were $1,279 million, an increase of 26% year-over-year. The sales were primarily driven by volume gains in the U.S. and strong uptake in key international markets like Europe and Japan.[98] Due to its novel mechanism of action, availability of oral dosage form and acceptable safety profile, apremilast has become fast growing molecule in psoriasis therapeutics in Indian drug market in a short span of 1 year.

Conclusion

In summary, apremilast is reasonably efficacious in psoriasis and PsA with potential clinical use in other inflammatory conditions. Good safety profile, ease of oral administration without a need for screening or ongoing laboratory monitoring makes it a well-sought drug among dermatologists. However, a low drug survival beyond 6–8 months as reported in recent real-world studies and a critical observation on cost-effectiveness by NICE experts necessitate a considered thought on its long-term use as a maintenance therapy. Availability of newer formulations as 10 and 20 mg widens the scope of its use in dose titrations in various settings. 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. PDE4 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.

Contributions

T.P.A. and M.R.T.: Acquisition of data, design of paper, writing the manuscript, final approval of article. S.D.: Concept and design of paper, critical revision, and intellectual input and final approval of article.

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Conflicts of interest

There are no conflicts of interest.

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