

## Research Article

# Apremilast in Patients Difficult to Treat: A Multicentric Real-Life Long-Term Experience

**Emanuele Trovato** <sup>1</sup>, **Eugenio Capalbo**,<sup>1</sup> **Alessandra Cartocci** <sup>2</sup>, **Gionata Buggiani**,<sup>3</sup> **Aldo Cuccia** <sup>4</sup>, **Alberto Ghilardi**,<sup>5</sup> **Salvatore Panduri**,<sup>6</sup> **Imma Savarese**,<sup>7</sup> **Serena Guiducci**,<sup>8</sup> and **Francesca Prignano**<sup>9</sup>

<sup>1</sup>Unit of Dermatology, Department of Medical, Surgical and Neurological Sciences, University of Siena, Siena, Italy

<sup>2</sup>Department of Medical Biotechnologies, University of Siena, Siena, Italy

<sup>3</sup>Unit of Dermatology, San Giuseppe Hospital, Empoli, Florence, Italy

<sup>4</sup>Unit of Dermatology, San Donato Hospital, Arezzo, Italy

<sup>5</sup>Unit of Dermatology, Hospital of Campo di Marte, Lucca, Italy

<sup>6</sup>Department of Dermatology, University of Pisa, Pisa, Italy

<sup>7</sup>Department of Dermatology, San Jacopo Hospital, Pistoia, Italy

<sup>8</sup>Department of Experimental and Clinical Medicine, Division of Rheumatology, University of Florence, Florence, Italy

<sup>9</sup>Section of Dermatology, Department of Health Sciences, University of Florence, Florence, Italy

Correspondence should be addressed to Alessandra Cartocci; [alessandra.cartocci@dbm.unisi.it](mailto:alessandra.cartocci@dbm.unisi.it)

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Psoriasis is an inflammatory disease nowadays considered not only as a cutaneous but also as a systemic disease. Systemic therapy plays a crucial role in the management of psoriasis. Apremilast is an inhibitor of phosphodiesterase-4 (PDE4), indicated in the treatment of moderate-to-severe psoriasis. Here, we report a multicentric case series of patients treated with apremilast with resolution of skin manifestations and maintenance of clinical response for a minimum of 2 years. By inhibiting PDE4, apremilast acts as a ubiquitous intracellular enzyme, whose active form degrades adenosine cyclic intracellular monophosphate (cAMP) into AMP. The increase in cAMP determines a decrease in proinflammatory cytokines such as TNF- $\alpha$ , IL-17, IL-23, and upregulation of IL-10 with an anti-inflammatory action. Considering the growing incidence of comorbidities in the world population and in particular the strict correlation in patients with psoriasis, it is important to identify therapeutic options able to avoid a negative impact on patients with both conditions. The aim of this work is to highlight the utility of this molecule in the long-term management of these patients. Moreover, these case series further underline the high safety profile and manageability of this small molecule.

## 1. Introduction

Psoriasis (PsO) is a chronic relapsing inflammatory T-cell-mediated disease due to a dysregulation of the immune system with an imbalance between proinflammatory and anti-inflammatory cytokines [1]. It is strictly related to multiple comorbidities, such as psoriatic arthritis (PsA) [2], obesity [3], metabolic syndrome (MetS) [4], cardiovascular diseases (CVDs) [4, 5], acute anterior uveitis [6], and

inflammatory bowel disease (IBD) [7]. PsA is a heterogeneous seronegative chronic inflammatory arthritis associated with psoriasis, which may manifest with different domains such as dactylitis, enthesitis, synovitis, and spondylitis [8]. The estimated prevalence of PsA in patients with psoriasis ranges widely between 7% and 42% [9, 10]. Patients with PsA are at higher risk of developing comorbidities with a significant impact on their quality of life [4]. Although the advanced knowledge of the pathogenetic mechanisms of PsO

and PsA helped in developing an abundant therapeutical armamentarium, the available drugs might still show a suboptimal efficacy [11]. Systemic therapy plays a crucial role in the management of psoriasis refractory to topical treatment only, with a wide range of options ranging from conventional disease-modifying antirheumatic drugs (cDMARDs) to small molecules and biological drugs. Several classes of biologics and small molecules have been approved for moderate-to-severe psoriasis, including targeted inhibitors of tumour necrosis factor (TNF) (infliximab, etanercept, adalimumab, and certolizumab pegol), interleukin (IL)-12/23 (ustekinumab), IL-17 (secukinumab and ixekizumab), IL-17 receptor (brodalumab), IL-23 (guselkumab, risankizumab, and tildrakizumab), and phosphodiesterase-4 (apremilast) [12]. Hence, the duty of dermatologists to develop a tailored therapy allows for achieving the best possible result against PsO, considering patients' comorbidities and compliances. Apremilast is an inhibitor of PDE4, a ubiquitous intracellular enzyme, whose active form degrades adenosine cyclic intracellular monophosphate (cAMP) into AMP. The increase in cAMP determines a decrease in proinflammatory cytokines such as TNF- $\alpha$ , IL-17, IL-23, and upregulation of IL-10 with an anti-inflammatory action [13]. Apremilast is available as oral therapy in tablets that are indicated in the treatment of moderate-to-severe psoriasis in those patients who have failed or are intolerant or with contraindications to cDMARDs and/or biologics. Apremilast is also indicated in combination with DMARDs, for the treatment of PsA in the active phase not responsive to DMARDs monotherapy, or as single therapy in patients with contraindication or intolerance to DMARDs alone [14, 15]. Here, we report a multicentric case series of patients treated with apremilast with resolution of skin manifestations and maintenance of clinical response for a minimum of 2 years. The aim of this work is to highlight the utility of this molecule in the long-term management of these patients. Moreover, these case series further underline the high safety profile and manageability of this small molecule.

## 2. Case Series

- (1) A 47-year-old woman came to our observation for psoriasis in the upper and lower limbs (PASI 8), present for about 10 years. No joint involvement was reported. The patient underwent phototherapy cycles (UVB narrow band and PUVA) with mild improvement. She reported a moderate impact of psoriasis on quality of life, especially related to the reduction in working hours. In personal history, arterial hypertension is not controlled by current drug therapy, pathological dry eye, cluster headache, irregular alveus, and altered lipid profile with hypertriglyceridemia and heterozygous familial hypercholesterolemia in treatment with evolocumab and statins. Considering anamnesis, comorbidities, and clinical manifestations, we decided to start therapy with apremilast according to the authorized dosing regimen with achievement of PASI75 at 16 weeks and PASI90 at 24 weeks with maintenance of the same up to week 202. No AEs were reported.
- (2) A 56-year-old man came to our department with a suberythrodermic psoriasis, involving almost 70% of the body area, and concomitant psoriatic arthritis. The patient did not refer to a relevant impact on quality of life, with a DLQI of 14. In anamnesis, arterial hypertension, diabetes mellitus, chronic renal failure, chronic HCV infection, and latent tuberculosis for which he underwent twice eradication therapy with isoniazid and rifampicin, suspended after 2 months for intolerance. We started apremilast 30 mg twice a day. At 12 weeks, he reported a clear-cut improvement of arthritis, but the skin was not clear, with PASI 8. The patient continued therapy with complete clear skin at week 36 and maintained the result at week 104. No AEs were reported.
- (3) We present the case of a man, 71 years old, who came to our attention in March 2009 with severe widespread psoriasis (PASI 43.3). The patient was diagnosed with hypercholesterolemia and obesity. The patient had already been treated with cyclosporine, infliximab, and efalizumab. We started therapy with etanercept 50 mg/week. After a positive result, he underwent secondary failure (PASI 13.2), and in January 2012, he started adalimumab until April 2014 when he came back to our department with PASI 17.2, and we switched to ustekinumab 90 mg. In September 2018, he was diagnosed with pulmonary non-small-cell lung carcinoma (NSCLC) and underwent surgery, radiotherapy, and chemotherapy. In February 2019, he came back to our department with PASI 20, so we started acitretin 25 mg. After 12 weeks, the patient did not reach PASI 50 and reported nausea, xerostomia, and xerophthalmia. In June 2020, after the failure of phototherapy, we decided for apremilast 30 mg twice a day with complete resolution of psoriasis (PASI 3). The results, at 108 weeks, are still unchanged, without any adverse events.
- (4) A woman, 67 years old, affected by psoriasis for 25 years, came to our attention in November 2019 with erythematous-desquamative manifestations widespread in the upper and lower limbs and the back (PASI12). The patient was diagnosed with hypertension, hypercholesterolemia, interventricular defect with left-right shunt, and breast cancer in December 2015. In February 2016, she started hormone therapy with letrozole. According to anamnesis and clinical manifestations, we decided to begin therapy with apremilast 30 mg twice a day. After 52 weeks, the patient reached PASI 90 with further improvement in January 2021 (PASI 1). At the last follow-up visit in August 2022, the results were still maintained with no adverse events.

- (5) We present the case of a 75-year-old man suffering from palmar pustular psoriasis for about 30 years and peripheral arthralgias for 7 years. The patient was diagnosed with chronic benign lymphocytosis, hypercholesterolemia in treatment with simvastatin, and hyperuricemia in treatment with allopurinol. For psoriasis, the patient had undergone cycles of UVB-NB phototherapy with mild benefit and therapy with acitretin, suspended for intolerance (diarrhoea and hair loss). Blood chemistry tests showed positivity for the QuantiFERON test. In January 2018, the patient began therapy with apremilast 30 mg twice daily. In April 2018, the patient reported great improvement of psoriasis. However, the onset of diarrhoea and abdominal pain, not controlled by antidiarrheal therapy, leads us to reduce the dosage to 30 mg once a day. In December 2018, complete resolution of clinical manifestations with the absence of gastroenteric symptoms, so we decided to further reduce apremilast to 30 mg every other day. In January 2019, the patient reported initial mild relaps of palmar pustular psoriasis, so he started again 30 mg twice a day. At 52 weeks, the patient had complete remission of the clinical picture and of the diarrhoea, and a condition also maintained at 220 weeks of therapy.
- (6) We present the case of a man, 48 years old, with palmar-plantar psoriasis diagnosed in 2016, for which he has undergone courses of topical therapy with mild benefit. In 2017, diagnosis of PsA so he started methotrexate. Regarding family history, the patient's children had atopic dermatitis. He also referred to a previous diagnosis of chronic obstructive pulmonary disease (COPD). In 2018, he began therapy with etanercept suspended after 12 weeks for secondary ineffectiveness and subsequently with ixekizumab suspended after 3 months for primary ineffectiveness and worsening of skin manifestations. Then, he began therapy with prednisone 25 mg 1 tablet per day and ceftazidime 1 gr 1 tablet  $\times$  2 times per day. In November 2018, we started therapy with apremilast 30 mg twice a day with complete remission of the picture at 36 weeks and maintenance of response at 224 weeks. No AEs were reported.
- (7) We report the case of a man, 58 years old, overweight (BMI 32.4) suffering from psoriasis for about 20 years. He was diagnosed with metabolic syndrome and hypertriglyceridemia (394 mg/dl) despite rosuvastatin and fenofibrate. The patient only underwent courses of topical therapy (betamethasone/calcipotriol) and UVB-nb phototherapy with mild benefit. PsA was diagnosed in 2018. In March 2000, HIV infection was currently being treated with abacavir/lamivudine and efavirenz, with CD4  $>$ 1000/mm<sup>3</sup> and undetectable viraemia. At clinical examination, PASI 10.2, BSA 12%, DLQI 20, VAS pruritus 7. Considering comorbidities and clinical manifestations, in February 2019, he started etanercept 50 mg/week, but it was stopped in June 2019 for primary ineffectiveness. In July 2019, he initiated apremilast. In August 2019, the patient reported diarrhoea resolved after 3 weeks, so we decided to continue therapy. In December 2019, PASI 4.1, BSA 6%, DLQI 8, VAS pruritus 3, and in May 2022, PASI 1.4, BSA 2%, DLQI 0, VAS pruritus 0, undetectable viraemia, CD4 1400/mm<sup>3</sup>. No opportunistic infections were reported.
- (8) We present the case of a woman, 76 years old, with psoriasis for about 25 years. She was only treated with cycles of local therapy (betamethasone/calcipotriol) and UVB-nb phototherapy with substantial benefit and recrudescence upon suspension. From March 2014 to June 2014, she did therapy with Cya 250 mg/day suspended for increased creatinine and hypercholesterolemia. From July 2014 to February 2015, therapy with acitretin 25 mg/day was suspended due to secondary ineffectiveness and telogen effluvium. In March 2015, uterus cancer was treated with surgery and chemotherapy. In September 2019: PASI 12, BSA 14%, DLQI 25, VAS pruritus 8, so we started therapy with apremilast according to induction scheme. No gastroenteric adverse effects were reported. In June 2021, she went to the emergency department for multiple erythematous papules and nodules and some purpuric lesions of the right leg for about 15 days, without any symptoms. The patient reported an accidental puncture with the thorns of a succulent plant at the level of the lateral malleolar region, about a month before the appearance of the lesions. The histological examination of the lesions revealed to be compatible with the diagnosis of nontuberculous mycobacteriosis, and *Mycobacterium chelonae* infection was detected on culture examination of lesional skin material. Based on the antibiogram, the patient was treated with clarithromycin 500 mg twice a day for 6 months with resolution of cutaneous lesions. The patient, however, continued apremilast without discontinuing therapy. In April 2022: PASI 0, BSA 0%, DLQI 2, VAS pruritus 0.

### 3. Results

The case series reported a cohort of 8 patients (5 men and 3 women) with PsO and/or PsA treated with apremilast 30 mg  $x^2$ /day with an induction scheme. The average age of the patients was  $62.25 \pm 10.9$  years. Six patients presented with vulgar psoriasis while 2 had palmoplantar pustular psoriasis. The median time from diagnosis was  $18.37 \pm 9.06$  years. Three patients were naïve to cDMARDs and biologics; the remaining five had been treated with cDMARDs alone (two patients) or with both cDMARDs and biologics (three patients) suspended for primary/secondary ineffectiveness or for the need of a switch following a new diagnosis of an

TABLE 1: Characteristics of all patients reported.

Patient	Gender	Age	Type of PsO	Particular sites	PsA	Duration of disease (years)	Comorbidities	Cancer	Infection
1	F	47	VP	—	No	10	Hypertension, pathological dry eye, cluster headache, irregular alveus, and altered lipid profile with hypertriglyceridemia and heterozygous familial hypercholesterolemia	—	—
2	M	56	Sub-eritrodermic	—	Yes	15	Arterial hypertension, diabetes mellitus, chronic renal failure, and chronic HCV infection	—	Latent tuberculosis
3	M	71	VP	—	No	25	Hypercholesterolemia and obesity	NSCLC	—
4	F	67	VP	—	No	25	Hypertension, hypercholesterolemia, and interventricular defect with left-right shunt	Breast	—
5	M	75	PP	Palms	No	30	—	—	Latent tuberculosis
6	M	48	VP	Palms	Yes	6	COPD	—	—
7	M	58	PP	—	Yes	20	Metabolic syndrome	—	HIV
8	F	76	VP	—	No	25	—	Uterus	—

VP: vulgar psoriasis, NSCLC: non-small-cell lung carcinoma, PP: pustular psoriasis, COPD: chronic obstructive pulmonary disease, MTX: methotrexate, CyA: cyclosporine A, PsA: psoriatic arthritis, PsO: psoriasis.

TABLE 2: Characteristics of all patients reported.

Patient	Previous cDMARDs	Previous biologics	PASI baseline	PASI last-follow-up	Weeks of therapy	AEs	Discontinuation for AEs	Other diseases during therapy
1	—	—	8	1	202	—	—	—
2	—	—	12	0	104	—	—	—
3	CyA, acitretin (after diagnosis of NSCLC)	Infliximab, efalizumab, etanercept, adalimumab, and ustekinumab	15	0	108	—	—	—
4	—	—	12	1	322	—	—	—
5	Acitretin	—	—	—	244	Diarrhoea	No	—
6	MTX and prednisone	Etanercept and ixekizumab	10.2	1.4	224	—	—	—
7	—	Etanercept	—	—	168	Diarrhoea	No	—
8	CyA and acitretin	—	12	0	208	—	No	Nontuberculous mycobacteriosis ( <i>Mycobacterium chelonae</i> )

AEs: adverse effects.

oncological nature. The most frequently reported adverse events were diarrhoea and nausea so it is mandatory to discuss it well with the patients to have their adherence to treatment. In the two patients with pustular psoriasis, it was possible to achieve PASI 0 and its maintenance after 1 year, and, specifically in the localized form, an initial response was recorded after two weeks with a transition from PASI 9 to PASI 6. In neoplastic patients not eligible for biological therapy, apremilast has given good results also considering that it is the only allowed molecule for PsO which can be exploited in the first 5 years of oncological diagnosis. In addition, excellent response was reported in the use of apremilast as switch therapy in the patient receiving ustekinumab but with a subsequent diagnosis of NSLCL. Only one patient had an opportunistic infection by *Mycobacterium chelonae* resolved after antibiotic therapy with clarithromycin without discontinuing apremilast. Within the cohort, there was also a patient with latent TB and a patient affected by HIV with undetectable viraemia after antiviral treatment with abacavir/lamivudine and efavirenz where apremilast proved to be effective, as well as safe; in fact, after about 3 years from the start of therapy, there was no worsening of the count or increased viraemia. Furthermore, no opportunistic infections were reported. All the patients and their characteristics are reported in Tables 1 and 2.

#### 4. Discussion

Apremilast is an inhibitor of PDE4, approved for the treatment of moderate-to-severe PsO and PsA. It induces an increase in cAMP improving homeostasis between proinflammatory and anti-inflammatory mediators [16]. This could contribute to the achievement of good efficacy results. All the cases reported in this paper showed peculiar characteristics useful to underline the role of apremilast among the possible therapeutic alternatives currently available for PsO. In the first case, all the possible therapies presented some critical points in the choice. In detail, the alteration of the patient's lipid profile excluded a therapy with cyclosporine and acitretin, as well as the irregular and tendentially diarrheal alveus cast doubts on the use of dimethyl fumarate. At the same time, therapy with ezetimibe for familial hypercholesterolemia could constitute a long-term risk factor for therapy with biologics, especially for anti-TNF. In this delicate balance, apremilast proved to be effective and safe, reaching the full satisfaction of the patient. Furthermore, apremilast has been an excellent therapeutic resource in terms of efficacy and safety even in the second patient with psoriasis and bilateral sacroillitis, as well as chronic HCV infection and latent TB with two unsuccessful attempts at eradication therapy, showing the high safety profile towards patients with infectious risk. Cases 5 and 6 reported patients with palmoplantar pustulosis with complete resolution under apremilast. Its clinical efficacy in addition to a favourable safety profile makes this treatment a future viable option for treating this population of patients. However, this hypothesis is just based on case reports [17] and should be confirmed by cohort studies. Among all our

patients, only one patient presented intolerable gastroenteric symptoms unresponsive to recadopril; in this patient, a dose reduction to 30 mg/day was required during the first post-induction treatment phase and 30 mg every other day in the maintenance phase, still reaching excellent levels of effectiveness. In HIV + patients, the dysregulation of T lymphocytes makes psoriasis difficult to manage, resulting in more severe and recalcitrant clinical forms. The treatment of psoriasis in these patients is challenging, not only due to virus-mediated immunosuppression but also due to the possible worsening of psoriasis and the infection itself [18]. Since HIV + patients are traditionally excluded from clinical trials, knowledge of monoclonal antibodies (mAbs) management in this population is mainly based on case reports and case series [19]. Elevated TNF levels have been shown to be associated with increased viral load, decreased CD4 count, and increased symptoms of HIV progression, such as fever, fatigue, cachexia, and dementia [20]. The same was also evident for patient no. 8 who developed a cutaneous mycobacterial infection with complete resolution with antibiotics without the need to discontinue therapy with apremilast. Finally, it is necessary to underline, once again, the relevant role of apremilast as therapy in cancer patients. To date, only apremilast has an indication in the technical data sheet in patients with cancer. This condition is undoubtedly linked to the unique mechanism of action and pharmacokinetics, which allow its use in particularly vulnerable patients. This has been widely demonstrated in clinical trials [21]. However, given the ever-increasing incidence of malignancies in the general population, there is an important number of real-world evidence works focused on these patients in the scientific literature. Bernardini et al. observed 28 patients with cancers treated with apremilast for 104 weeks, showing efficacy on both PASI and BSA and without reporting adverse effects [22]. Tsentemeidou et al. in a systematic review reported 37 patients with both solid and blood malignancies treated with apremilast with high efficacy and mild side effects [23]. The same results were reported in a recent French real-world multicenter study [24]. A particular mention should be reserved for patients in therapy with immune checkpoint inhibitors, which are significantly increasing, where apremilast proved to be an effective and safe option for the treatment of psoriasis [25].

#### 5. Conclusion

The reported cases allow us to highlight the manageability of apremilast and the evident data in terms of efficacy and safety. Gastrointestinal side effects, although common, have never been so relevant to require the suspension of therapy with resolution in about two weeks from onset. Furthermore, in the most resistant cases, the reduction of the apremilast dosage from two cp/day to one cp/day allowed an improvement in diarrhoea without altering the clinical efficacy in terms of PASI reduction, both in the short and long term. We believe that larger cohort studies are needed, especially in real-world patients to further confirm the role

of apremilast and to modify, where possible, its positioning in the current therapeutic algorithm.

### Data Availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

### Conflicts of Interest

The authors declare that there are no conflicts of interest.

### Authors' Contributions

Emanuele Trovato and Eugenio Capalbo wrote the manuscript and prepared the original draft, and Francesca Prignano reviewed and edited the manuscript. All authors have read and agreed the published version of the manuscript.

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