MOLECULE MICI, SPERANȚE MARI PENTRU PACIENȚII CU PSORIAZIS ÎN TRATAMENT CU APREMILAST!

SMALL MOLECULES, BIG EXPECTATIONS FOR PATIENTS WITH PSORIASIS ON APREMILAST

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Rezumat

Boala psoriazică este o afecțiune inflamatorie cronică cu un impact serios asupra sănătății. Mecanismele bolii implică modificări inflamatorii locale, dar și sistemice.

Apremilast este un inhibitor selectiv de fosfodiesterază 4 (PDE4) oral, care reglează mai mulți mediatori ai inflamației implicați în patogeneza bolii psoriazice, precum factorul de necroză tumorală (TNF) alfa, interleukina 10 (IL 10) sau interleukina 23 (IL23), unele dintre cele mai importante citokine implicate.

Deși există o gamă largă de opțiuni terapeutice, începând cu terapiile topice și continuând cu terapiile modificatoare de boală (DMARDs), apremilast își găsește locul atât în cazurile moderat-severe de psoriazis, dar mai important, in cazuri speciale ale pacienților cu psoriazis care nu sunt eligibili sau nu au răspuns la celelalte clase de medicamente.

Cuvinte chei:*e apremilast, psoriazis, zone dificil de tratat.*

Intrat în redacție: 21.08.2023
Acceptat: 22.09.2023

Summary

Psoriatic disease is a chronic inflammatory disease with a serious impact on the health of affected individuals. The mechanisms of the disease involve local but also systemic inflammatory changes.

Apremilast is a selective oral phosphodiesterase 4 (PDE4) inhibitor, which regulates many inflammatory mediators involved in the pathogenesis of psoriatic disease, such as tumor necrosis factor (TNF alfa), interleukin 10 (IL-10) or interleukin 23 (IL-23), some of the most important interleukins in psoriasis.

Although there is currently a wide range of therapeutic options, starting from topical therapies and going to disease-modifying antirheumatic drugs (DMARDs), apremilast finds its indications both in common cases of moderate-severe psoriatic disease, but more importantly, in special cases of patients with psoriatic disease who are not eligible or have not responded to other therapies.

Key words*: apremilast, psoriasis, difficult-to-treat areas.*

Received: 21.08.2023
Accepted: 22.09.2023

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1. Background

Psoriasis is a chronic inflammatory disease predominantly affecting the skin and is estimated to occur in 2–3% of the population [1]. A subset of these patients with psoriasis will also develop psoriatic arthritis, a seronegative spondyloarthropathy with five clinical disease patterns: distal, oligoarticular, polyarticular, primarily axial, and arthritis mutilans, with a prevalence of 0.3–1.0%, affecting up to 30% of patients with cutaneous psoriasis [2,3,4].

Disease mechanisms involve local and systemic chronic inflammatory processes [3]. The hallmark of psoriasis is sustained inflammation that leads to uncontrolled keratinocyte proliferation and dysfunctional differentiation [5]. One of the proposed mechanisms involves the recognition of antimicrobial peptides (AMPs), which are secreted by keratinocytes in response to injury and are characteristically overexpressed in psoriatic skin. The activation of peripheral dendritic cell (pDC) is key in starting the development of the psoriatic plaque and is characterized by the production of type I IFN [5,6].

Type I IFN signaling promotes the phenotypic maturation of myeloid dendritic cells (mDC) phenotypic maturation and has been implicated in Th1 and Th17 differentiation and function, including the production of IFN-γ and interleukin (IL)-17, respectively [6,7,8]. Activated mDCs migrate into draining lymph nodes and secrete tumor necrosis factor (TNF)-α, IL-23, and IL-12, the latter two modulating the differentiation and proliferation of Th17 and Th1 cell subsets, respectively [5].

The TNFα–IL-23–Th17 inflammatory pathway characterizes plaque-type psoriasis. The pathogenesis of psoriasis can be conceptualized in an initiation phase possibly triggered by trauma (Koebner phenomenon), infection or drugs, and a maintenance phase characterized by a chronic clinical progression [5].

Current treatment recommendations for patients with psoriasis depend on the severity of the disease. Mild disease is treated with topical therapies (corticosteroids, vitamin D analogues, tazarotene) alone or in combination with phototherapy and/or traditional nonbiologic systemic therapy (methotrexate, cyclosporine, acitretin) [9,10,11]. Moderate-to-severe disease typically requires the use of systemic agents, whether traditional or biologic agents [10,12].

Apremilast is chemically identified as N-[2-[(1S)-1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl) ethyl]-2,3-dihydro-1,3-dioxo-1H-isoindol-4-yl] acetamide. The molecular formula and weight of apremilast are C22H24N2O7S and 460.5 g/mol, respectively [12]. By inhibiting PDE4, apremilast prevents the degradation of cyclic adenosine monophosphate (cAMP). The subsequent increased level of cAMP results in an antagonistic effect on the production of proinflammatory cytokines such as TNF-α, IL-23, and interferon (IFN)-γ, and an increase in anti-inflammatory mediators (IL-10) [3,13].

Apremilast is approved in the European Union for the treatment of moderate-to-severe chronic plaque psoriasis in adult patients who failed to respond to or who have a contraindication to, or are intolerant of other systemic therapy including cyclosporine, methotrexate or psoralen and ultraviolet-A light (PUVA). Other indications include psoriatic arthritis and Behçet's disease [14].

The initial dose on day 1 is 10 mg in the morning; this is increased to 10 mg in the morning and evening on day 2. The evening dose is further increased by 10 mg (to 20 mg) on day 3. On day 4, the morning dose is increased to 20 mg such that 20 mg is taken twice daily, and on day 5 the evening dose is increased to 30 mg. The maintenance dose of 30 mg twice daily begins on day 6 [3]. Patients with severe renal impairment (creatinine clearance less than 30 mL/min as estimated by the Cockcroft–Gault equation) require a modified dosing schedule with a maintenance dose of 30 mg once daily. When titrating the initial dose in such individuals, it is recommended to eliminate the evening dose [3].

2. Clinical cases

In this case series report developed by the authors, 7 patients, 4 women and 3 men, all diagnosed with psoriasis with palmoplantar involvement and treated with apremilast were included. These patients were included in the National Registry of Dermato-Venereal Diseases

and signed the informed consent to participate in this case series report.

In what follows, we will present a case series report of 7 patients with psoriasis vulgaris, hard-to-treat due to the clinical peculiarities. We will briefly describe each patient with their clinical characteristics and disease severity scores before initiation of treatment with apremilast and 3 months after initiation of this therapy.

The first case is that of a 62-year-old female patient, with multiple comorbidities: hypertension, chronic hepatitis C, morbid obesity, impaired glucose tolerance, surgically corrected anterior communicating artery and middle cerebral artery aneurysms. The patient was diagnosed in 2015 with psoriasis vulgaris, moderate form, affecting special areas – palmoplantar, nails and scalp, reflected by the following initial severity scores: PASI 11.2, DLQI 18, ESIF 36, NAPSI 53, PSSI 3. Over the years, the patient underwent multiple treatments – topical corticosteroids, emollients, conventional systemic therapy with methotrexate, short courses of neotigason and biological therapy with ixekizumab and guselkumab. Unfortunately, none of the therapies helped the patient.

The second case is the case of a 59-year-old female, with no significant personal pathological history at the onset of psoriasis (1998). The patient was diagnosed in 2022 with psoriasis vulgaris, moderate form, affecting special areas, palms and soles, reflected by the following initial severity scores: PASI 18.2, DLQI 17, ESIF 22. The patient underwent treatments with topical corticosteroids, emollients, conventional systemic therapy with methotrexate, without any clinical benefit.

The third case is the case of a 63-year-old woman with dyslipidemia and chronic venous disease. The onset of psoriasis was in 2000, but the patient was diagnosed in 2022 with psoriasis vulgaris, moderate form, affecting special areas – palms and soles. The severity of the disease was reflected by the following initial severity scores: PASI 10.8, DLQI 24, ESIF 28. The patient underwent treatments with topical corticosteroids, emollients, conventional systemic therapy with methotrexate, without any clinical benefit.

The fourth patient was a 47-year-old female with no significant personal pathological history at the onset of psoriasis (2021). The patient was diagnosed in 2022 with psoriasis vulgaris, moderate form, affecting special areas – palmoplantar and scalp, reflected by the following initial severity scores: PASI 10.2, DLQI 29, ESIF 28, PSSI 21. The patient underwent treatments with topical corticosteroids, emollients, conventional systemic therapy with methotrexate, without any clinical benefit.

The fifth case is of a 55-year-old male, with multiple comorbidities: grade II arterial hypertension, haemorrhagic stroke with left hemiparesis, convulsive seizures, operated bilateral inguinal hernia and gastro-oesophageal reflux disease. The psoriasis onset was in 1997, but the patient was diagnosed in 2022 with psoriasis vulgaris, moderate form, with the following initial severity scores: PASI 10.6, DLQI 12. The patient underwent treatments with topical corticosteroids, emollients, conventional systemic therapy with methotrexate, with minimal clinical improvement.

The sixth case is of a 74-year-old male patient, with no significant personal pathological history at the onset of psoriasis (2018). The initial severity scores were: PASI 20.8 and DLQI 15. The patient received treatments with topical corticosteroids, emollients, conventional systemic therapy with methotrexate, biological therapy with ixekizumab, but in 2021 he was diagnosed with prostatic adenocarcinoma, therefore the biological therapy had to be stopped. After a period of time, approximately 4 months, the patient returned to our clinic with "blooming" psoriasis with the following severity scores: PASI 22 and DLQI 20.

The seventh case is of a 51-year-old male patient with hypertension and pulmonary sequelae of tuberculosis. The patient presented in our clinic with erythrodermic psoriasis with pustulation and affecting special areas: palmoplantar and nails. The initial severity scores were: PASI 41.1, DLQI 23, NAPSI 114 and PSSI 27. The patient underwent treatments with topical corticosteroids, emollients, conventional systemic therapy with methotrexate, phototherapy, but the clinical benefits were minimal.

Through the prism of the particularities of these 7 cases presented, we can summarize the following: patients numbers 1-4 had palmoplantar involvement, a hard-to-treat area, without a special treatment dedicated to this area and they were unresponsive to previously recommended treatments (topical, systemic conventional but also biological); patient number 5 did not want injectable treatment; patient number 6 was diagnosed with neoplasia; patient number 7 had pulmonary sequelae of tuberculosis.

Many factors must be considered when selecting the optimal therapy for patients with plaque psoriasis. There is a need for effective and well-tolerated systemic therapies for these patients with moderate to severe psoriasis. [15]

We decided to treat them taking into account the aspects presented above and we concluded that the most appropriate treatment for each individual patient was represented by apremilast. At the 3-month follow-up visit, we evaluated the patients clinically and paraclinically (complete blood count, erythrocyte sedimentation rate, renal and liver tests, fasting blood glucose, lipid panel and electrolytes), with no new changes observed in any patient's biological samples. The big surprise was at the clinical evaluation, when we noticed a significant improvement in all patients, even in those patients with the involvement of special areas which was reflected in the disease severity scores.

For a succinct and clear presentation of these patients, we have created the table below (Table 1), which lists the main characteristics.

Table 1. The main characteristics of the studied patient group

No.	Sex	Age	Psoriasis onset	Psoriasis diagnosis	Personal pathological history	Previous treatments	Severity scores before starting apremilast	Severity scores after 3 months of apremilast
1	F	62	unknown	2015	hypertension, chronic hepatitis C, morbid obesity, altered glucose tolerance, anterior communicating artery and middle cerebral artery aneurysms surgically corrected	topical corticosteroids and emollients, methotrexate, neotigason, ixekizumab, guselkumab	PASI 11.2 DLQI 18 ESIF 36 NAPSI 53 PSSI 3	PASI 2.6 DLQI 7 ESIF 14 NAPSI 43 PSSI 0
2	F	59	1998	2022	none	topical corticosteroids and emollients, methotrexate	PASI 18.2 DLQI 17 ESIF 22	PASI 9.8 DLQI 1 ESIF 10
3	F	63	2000	2022	dyslipidemia, chronic venous disease	topical corticosteroids and emollients, methotrexate	PASI 10.8 DLQI 24 ESIF 28	PASI 2.6 DLQI 13 ESIF 12
4	F	47	2021	2022	none	topical corticosteroids and emollients, methotrexate	PASI 10.2 DLQI 29 ESIF 28 PSSI 21	PASI 3.8 DLQI 12 ESIF 16 PSSI 0
5	M	55	1997	2022	arterial hypertension, hem-	topical	PASI 10.6 DLQI 12	PASI 3.8 DLQI 4

					orrhagic stroke, left hemiparesis, convulsive seizures, operated bilateral inguinal hernia, gastro-oesophageal reflux disease	corticosteroids and emollients, methotrexate		
6	M	74	2018	2018	prostatic adenocarcinoma	topical corticosteroids and emollients, methotrexate, ixekizumab	PASI 22 DLQI 20	PASI 3.1 DLQI 2
7	M	51	unknown	2021	hypertension, pulmonary sequelae of tuberculosis	topical corticosteroids and emollients, methotrexate, phototherapy	PASI 41.4 DLQI 23 NAPSI 114 PSSI 27	PASI 18 DLQI 7 NAPSI 98 PSSI 13

3. **Discussions**

As we can see, there was a significant clinical improvement for each patient, which is mirrored by the severity scores, even in patients with significant, debilitating palmoplantar involvement; similar results can be seen in the EMBRACE trial performed on patients from Western Europe [16] or in a meta-analysis conducted in 2022 [17]. These patients had a low quality of life, they were not able to exercise ordinary things with their hands, because almost every movement was painful, accompanied by small bleeding from the fissures. At first presentation in our medical office, 3 out of 4 patients with palmar lesions were wearing gloves (both for fear of being stigmatized and for fear of microbial superinfection of the lesions).

Patients also complained of pain while walking, with one patient (the first patient) stating that she became dependent on her daughter - the patient could only move for short distances (a few meters). At the 3-month visit, patients stated that they were able to stop wearing gloves, could perform tasks using their hands almost as well as before the onset of the disease because the pain decreased significantly. We noticed the disappearance of fissures in palms and soles. Patients' gait was also improved, with minimal, inconstant pain. The patient who was dependent on her daughter became independent. This was possible due to the remarkable improvement of the disease, as can be seen in the first figure (Figure 1).

The patient who did not want injectable treatment experienced significant clinical improvement and expressed satisfaction with the administration of the treatment. For the sixth patient with prostate adenocarcinoma, the most disturbing thing regarding the psoriasis was represented by intense itching, the most annoying he had ever had in his life, possibly exarcebated by the medical condition added to the psoriasis. At the 3-month visit, the patient was symptom-free and the rash had almost faded. Regarding the last patient, the clinical improvement was spectacular, with relief of itching and significant clearing of the skin lesions, as can be seen in the second figure (Figure 2).

Three of the patients had arterial hypertension. Beta-blockers are a commonly prescribed medication, but can exacerbate pre-existing psoriasis and sometimes induce psoriasis [18,19,20]. The last patient with hypertension, the 51-year-old male, did not have any antihypertensive treatment at his first presentation in our clinic, therefore, upon discharge from the

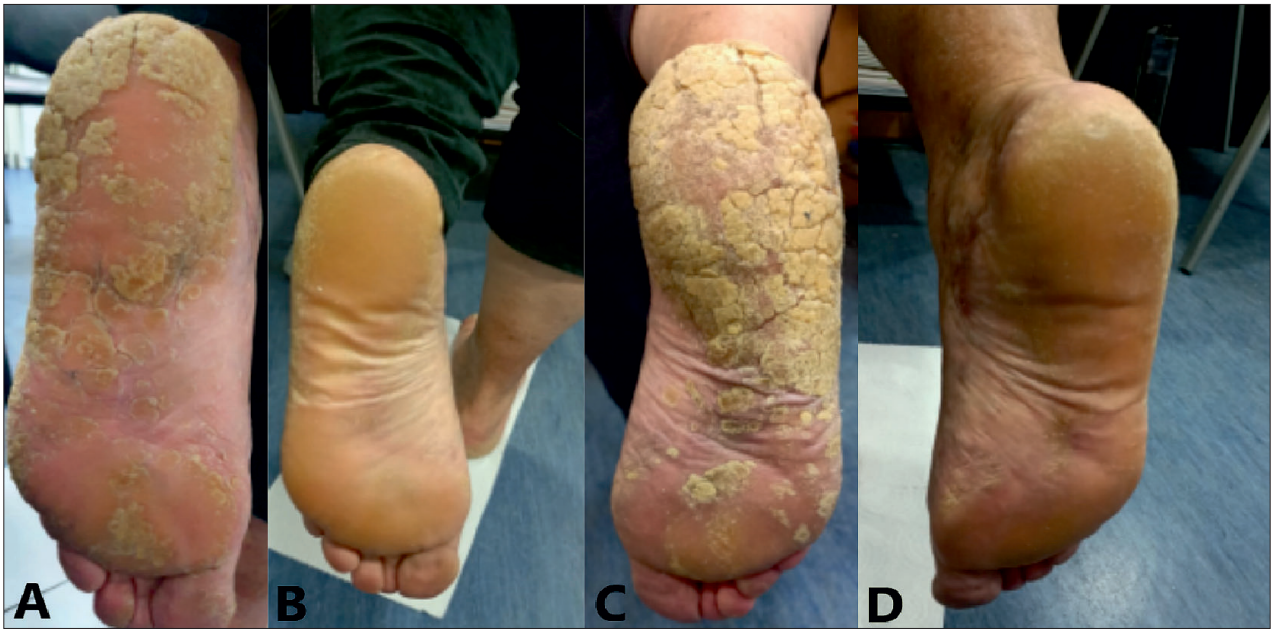

Figure 1. Pictures A and C were taken before treatment with apremilast, respectively picture B and D after treatment with apremilast.

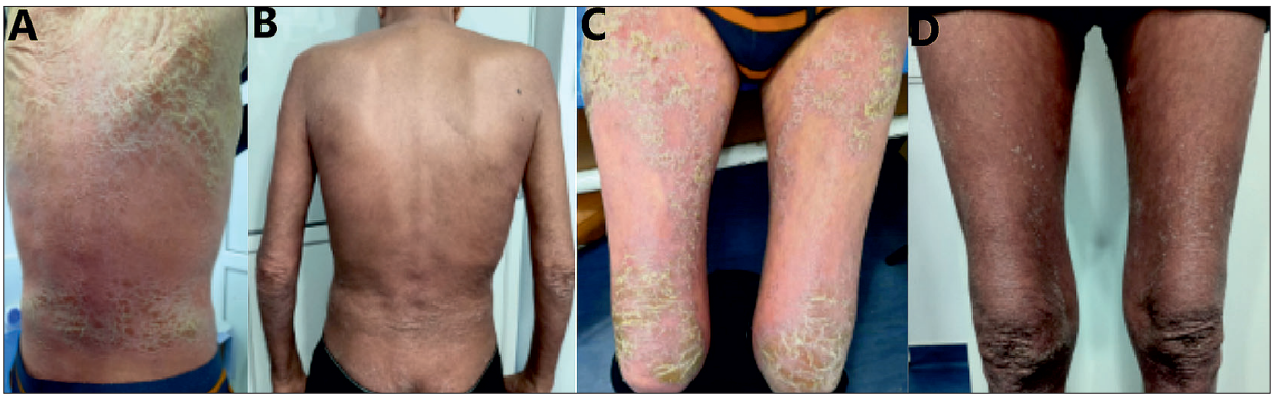

Figure 2. Pictures A and C were taken before treatment with apremilast, respectively picture B and D after treatment with apremilast.

hospital, he received a recommendation for a cardiological consultation in order to start an antihypertensive treatment, avoiding the prescription of beta-blockers antihypertensive classes by the cardiologist. The 55-year-old male with arterial hypertension was treated for this pathology, but fortunately there were no beta-blockers in the therapeutic regimen. The 62-year-old female patient, with multiple comorbidities, including hypertension, was under treatment with beta-blockers at her first medical visit in our department. At that very visit we recommended switching beta-blockers to other classes of antihypertensives and explained that the use of beta-blockers is known to exacerbate pre-existing psoriasis [21,22]. Although the antihypertensive treatment was changed, no improvement in psoriasis was observed.

Regarding psoriatic disease, nail psoriasis was observed in 2 of the 7 patients, and psoriatic arthritis was present in 4 of the 7 patients. All 4 patients complained of constant joint pain, and

nail involvement is a visible indicator to predict future joint inflammatory lesions and disease activity [23]. Our patients presented nail changes such as pitting, nail discoloration, subungual hyperkeratosis and onycholysis, with more than 3 nails affected, thus severe nail damage. Nail psoriasis is considered a significant psychological and social problem that causes functional impairment in affected patients [24]. Biological therapy is a great achievement in the treatment of nail psoriasis. The recommendations for therapy, in descending order of effectiveness, are represented by adalimumab, etanercept, ustekinumab, infliximab, apremilast and golimumab [25, 26, 27, 28]. Nail improvements were remarkable and were objectived with the NAPSI score. As can be seen, although therapeutic options for these patients were limited, we can state that apremilast is a therapeutic agent to consider in nail psoriasis. Moreover, the joint pain was relieved in 3 patients although we would like to specify the fact that the pain persisted in the 62-year-old female, with morbid obesity and most likely also a degenerative articular component.

It was really difficult for us to choose the most representative pictures of the patients showing their favorable evolution under this treatment, given that each patient had an unexpectedly good evolution.

Both for us, but especially for the patients, the choice of therapy proved to be the best, primarily by the significant improvement of the disease and secondly by the speed of the onset of the effect, not expecting to see such a significant improvement at the 3-month medical reassessment.

In addition to the already known advantages of apremilast, it comes with another possible benefit in the future: it appears to be suitable for aerosol administration. This possible administration would eliminate a disadvantage of this therapy, namely the speed of action. However, future experiments need to provide data for a reason to use this method of administration for different types of psoriasis and for different populations. [29,30].

4. Conclusions

In our medical practice, apremilast has earned our trust and, moreover, exceeded our expectations. It proved to be a reliable ally especially in the first case where we used the entire therapeutic arsenal without a satisfactory clinical response.

It has also been useful in the treatment of psoriasis in hard-to-treat areas, such as palmoplantar and scalp psoriasis. Moreover, the clinical response was rapid, with remarkable results from the first follow-up visit.

Furthermore, it is the only available molecule with which we can help patients with moderate-severe psoriasis and neoplasia.

Moreover, apremilast can be considered in patients with a history of tuberculosis, and last but not least, it is an oral therapy, available for patients who do not want injectable therapies.

5. Patents

Funding This research received no external funding.

Disclosure The authors declare no conflicts of interest.

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Conflict de interese
NEDECLARATE

Conflict of interest
NONE DECLARED

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