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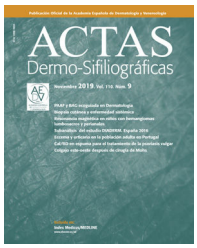

REVIEW

[Translated aticle] Topical and Oral Roflumilast in Dermatology: A Narrative Review

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KEYWORDS
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Abstract Oral roflumilast is a phosphodiesterase-4 inhibitor approved for the prevention of exacerbations of chronic obstructive pulmonary disease and chronic bronchitis. In dermatology, topical roflumilast is authorized by the US Food and Drug Administration for the treatment of plaque psoriasis and mild to moderate seborrheic dermatitis. Several studies have described the off-label use of roflumilast in dermatology, including a randomized controlled trial showing its usefulness in the treatment of psoriasis; case reports and small series have also reported successful outcomes in hidradenitis suppurativa, recurrent oral aphthosis, nummular eczema, lichen planus, and Behçet disease. Roflumilast has a favorable safety profile, similar to that of apremilast, and it is considerably cheaper than new generation drugs and even some conventional immunosuppressants. We review the pharmacokinetics and pharmacodynamics of topical and oral roflumilast and discuss potential adverse effects and both approved and off-label uses in dermatology. Roflumilast is a promising agent to consider.

PALABRAS CLAVE
Roflumilast;
Dermatología;
Psoriasis;
Apremilast;
Fosfodiesterasa;
Off-label

Roflumilast tópico y oral en dermatología. Una revisión narrativa

Resumen Roflumilast es un inhibidor de la fosfodiesterasa-4 aprobado de forma oral para la prevención de exacerbaciones en pacientes con enfermedad pulmonar obstructiva crónica y fenotipo de bronquitis crónica. En dermatología, el roflumilast tópico está aprobado por la *Food and Drug Administration* en psoriasis en placas y dermatitis seborreica leve/moderada. En cuanto a su uso fuera de indicación, hemos encontrado un ensayo clínico que avala la utilidad del roflumilast oral en psoriasis, así como pequeñas series de casos o casos clínicos aislados en hidradenitis supurativa, aftosis oral recurrente, eccema numular, liquen plano y enfermedad

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de Behçet. Su perfil de seguridad es favorable, similar al del apremilast, y su coste es considerablemente inferior a los de los fármacos de nueva generación, o incluso al de algunos inmunosupresores clásicos. Presentamos una revisión de roflumilast tópico y oral, en términos de farmacocinética y farmacodinámica, efectos adversos, usos dermatológicos aprobados y fuera de indicación. Roflumilast es un agente prometedor en dermatología.

Introduction

The arrival of biologic drugs and small molecules has revolutionized the management of multiple inflammatory dermatoses such as psoriasis, atopic dermatitis, hidradenitis suppurativa, and alopecia areata, among others. However, their high cost poses a significant limitation, especially when used off-label.[1]

Apremilast is an oral inhibitor of the enzyme phosphodiesterase-4 (PDE4), with immunomodulatory effects and no immunosuppression. It has been approved by the U.S. Food and Drug Administration (FDA) for the management of psoriasis,[2] psoriatic arthritis, and oral ulcers in patients with Behçet's disease.[3] Its safety profile is just excellent and has been successfully used off-label to treat multiple dermatoses.[3] Crisaborole is a topical PDE4 inhibitor approved to treat atopic dermatitis.[4] Roflumilast is another PDE4 inhibitor (PDE4i). Its oral form was initially approved by the European Medicines Agency (EMA) and the FDA to reduce the risk of exacerbations in chronic obstructive pulmonary disease (COPD) and chronic bronchitis phenotype.[5] Topical roflumilast cream at 0.3% was approved by the FDA in 2022 to treat of plaque psoriasis in patients older than 12 years, making it the first topical PDE4 inhibitor to be approved for the management of plaque psoriasis.[6] Back in April 2023, the FDA approved its topical use at 0.3% to treat seborrheic dermatitis.[7] Thanks to its excellent safety profile, ease of dosing, and low cost (the price of oral roflumilast is around €35/month in Spain), this drug has been used orally to treat plaque psoriasis, recurrent oral aphthosis, hidradenitis suppurativa, nummular eczema, and lichen planus, among other dermatoses. Its potential uses are not only limited to the dermatology setting, but also extend to cognitive impairment, dementia, schizophrenia, and other neurological or psychiatric conditions,[8–13] ulcerative colitis, diabetes mellitus, obesity, polycystic ovary syndrome, asthma, bronchiectasis, and cystic fibrosis[14–19] (table 1). In this article, we'll go over the mechanism of action, pharmacokinetics, long-term safety profile, and especially off-label uses of roflumilast in dermatology. We'll also discuss diseases that could potentially benefit from this drug due to its similar mechanism of action compred to apremilast.

Material and methods

We conducted a narrative review of the scientific medical literature currently available. Searches were performed on Medline and Google Scholar in the months of May and June 2023 using the following keyterms: ''roflumilast,'' ''dermatology,'' ''skin,'' ''off-label,'' ''safety,'' ''apremilast,'' ''phosphodiesterase,'' ''phosphodiesterase 4,'' ''psoriasis,'' ''atopy,'' ''atopic dermatitis,'' ''eczema,'' ''hand eczema,'' ''nummular eczema,'' ''ulcers,'' ''oral ulcers,'' ''aphthous stomatitis,'' ''oral aphthosis,'' ''lichen planus,'' ''seborrheic dermatitis,'' ''hidradenitis,'' ''hidradenitis suppurativa,'' ''vitiligo,'' ''alopecia areata,'' ''sarcoidosis,'' ''Behçet's,'' and ''morphea.'' This search was conducted among articles both written in Spanish and English. These articles were screened based on their abstracts, and selected according to their relevance after reading the studies. Similarly, a search with the keyterm ''roflumilast'' was conducted on clinicaltrials.gov. Two authors (MMP, and DMC) performed the search and article selection.

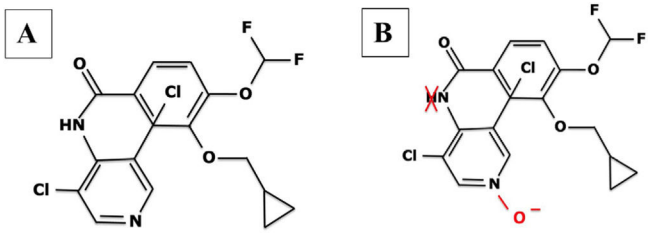

Figure 1 Biochemical structure of roflumilast (A) and its active metabolite, roflumilast N-oxide (B). Note the addition of an oxygen radical in the active form to one of the peripheral hexagonal rings and the removal of a proton in the middle ring (highlighted in red).

Roflumilast pharmacokinetics and mechanism of action

Pharmacokinetics (table 2)

When administered orally, roflumilast is completely absorbed by the GI tract, and its bioavailability stands at nearly 80%, reching its maximum plasma concentration within 1 hour after its administration.[20] (table 2). Regarding its metabolism, roflumilast is mainly hepatically metabolized by cytochromes CYP1A2 and CYP3A4, which turn the initial compound into the active metabolite roflumilast N-oxide (figure 1 [21]), whih is > 90% of roflumilast overall PDE4 inhibitory activity.[22] The original and active metabolites of roflumilast mainly bind to plasma proteins

Table 1 Uses of roflumilast in non-dermatological diseases.[8,38,80-86]

Clinical signs	Disease and study endpoints	Type of study	Primary reference
Pulmonary	Prevention of COPD exacerbations, phenotype CB (only approved use)	Completed randomized clinical trials (stage IV) NCT00297102 and NCT00297115	14
	Prevention of asthma exacerbations	Completed randomized clinical trials (stage III) NCT01365533	15
	Improvement of thr asthma-COPD overlap syndrome	Narrative literature review	16
	Reduction of chronic cough	Completed randomized clinical trials (stage IV) NCT01443845	17
	Prevention of exacerbations in bronchiectasis	Completed randomized clinical trials (stage III) NCT01580748	18
	Relief in symptomatic COVID-19-related infection	Narrative literature review. Unregistered in clinicaltrials.gov	19
Oncological	Improvement in association with conventional chemotherapy in diffuse large B-cell lymphoma	In vitro and animal studies (stage I) NCT03458546	38
Traumatological	Optimization of walking in spinal cord injuries	In vitro and animal studies (stage I)	80
Neuropsychiatric	Reduction of cognitive impairment and Alzheimer's disease	Ongoing randomized clinical trials (stage II) NCT04658654	8
	Improvement in schizophrenia	Ongoing randomized clinical trials (stage I) NCT02079844	9
	Fewer depressive symptoms as an adjuvant to other antidepressants	Ongoing randomized clinical trials (stage II) NCT04751071	10
	Reduction of peripheral neuropathy	Completed non-randomized clinical trial (stage II) NCT05884281	11
	Improvement of fragile X syndrome compared to baclofen and metformin	Uncompleted randomized clinical trial (stage II) NCT05163808	12
	Reduction of alcohol consumption in vitro	Completed non-randomized clinical trial (stage I). Unregistered in clinicaltrials.gov	13
Digestive	Potential reduction of ulcerative colitis flares	Ongoing clinical trial (stage I) NCT05684484	81
	Evaluation of roflumilast vs pioglitazone in non-alcoholic steatohepatitis	Completed randomized clinical trial (stage II) NCT01703260	82
Endocrinological	Use of roflumilast in type II diabetes	Completed randomized clinical trial (stage II) NCT01140542	83
	Reduction of insulin and glucose levels in obese prediabetic patients	Completed non-randomized clinical trial (stage II) NCT01862029	41
	Improvement of polycystic ovary syndrome compared to metformin	Completed non-randomized clinical trial (stage IV) NCT02037672	84
	Reduction of diabetic neuropathy compared to alpha-lipoic acid	Completed non-randomized clinical trial (stage III) NCT05369793	85
Renal	Improvement of analytical parameters of diabetic nephropathy	Completed non-randomized clinical trial (stage III) NCT04755946	86

CB, chronic bronchitis; COPD, chronic obstructive pulmonary disease.

Table 2 Characteristics of roflumilast.[8,38,41,80-86]

Item	Oral roflumilast	Topical roflumilast
Indications approved by the FDA	Prevention of COPD exacerbations, phenotype CB	Plaque psoriasis Seborrheic dermatitis
Pharmacokinetics	→ Oral bioavailability: 80% → Half-life: between 17 and 30 hours → Metabolism: almost exclusively hepatic. Conversion to active metabolite N-oxide → Excretion: 70% renal	→ Possibility of systemic absorption → Half-life around 24 hours → Metabolism: almost exclusively hepatic. Conversion to active metabolite N-oxide → Excretion: cutaneous and the absorbed systemic portion, mostly renal
Dosage	250 μg/day for 28 days followed by 500 μg/day for maintenance	Application of a thin layer to affected lesions. Approved at a concentration of 0.3%
Administration	Oral with or without food, diluted in water	1 application/day (thin layer). Avoid in ocular, oral, or intravaginal region
Contraindications	Hypersensitivity to the active substance or to any of its excipients.[a] Moderate or severe hepatic impairment (Child-Pugh class B or C)	Hypersensitivity to the active substance or any of its excipients.[a] Moderate or severe hepatic impairment (Child-Pugh class B or C)
Pharmacological interactions	Mainly metabolized by cytochromes CYP3A4 and CYP1A2. May require dose titration in patients with inducers or inhibitors of these cytochromes. The use of contraception with gestodene and ethinylestradiol can increase its toxicity.[b]	Mainly metabolized by cytochromes CYP3A4 and CYP1A2. May require dose titration in patients with inducers or inhibitors of these cytochromes. The use of contraception with gestodene and ethinylestradiol can increase its toxicity.[b]
Titration in liver failure	Caution in mild liver failure (Child-Pugh class A) and contraindicated in moderate or severe liver failure (Child-Pugh class B or C)	Caution in mild liver failure (Child-Pugh class A) and contraindicated in moderate or severe liver failure (Child-Pugh class B or C)
Titration in kidney disease	No dose titration required	No dose titration required
Titration in elderly patients	No dose titration required	No dose titration required
Pregnancy	Data on the use of roflumilast in pregnant women are scarce. Animal studies have shown reproductive toxicity, which is why its use in pregnant women is ill-advised	Data on the use of roflumilast in pregnant women are scarce. Animal studies have shown reproductive toxicity, which is why its use in pregnant women is ill-advised
Contraception	Women of childbearing age should use effective contraception methods during treatment. Avoid gestodene and ethinylestradiol[b]	May be considered if necessary. Avoid gestodene and ethinylestradiol[b]
Breastfeeding	Pharmacokinetic data available in animals reveal that roflumilast or its metabolites are excreted through breast milk, which is why its use in pregnant women is ill-advised	Possible. Avoid application in the breast area during application
Pediatric	Approved in kids ≥ 12 years. No studies have assessed its efficacy in kids < 12 years	Approved in kids ≥ 12 years. No studies have assessed its efficacy in kids < 12 years
Follow-up	Periodic reviews of weight and mood swings (every 3 to 6 months). No specification of blood tests during follow-up by the FDA and EMA. Recommended baseline blood tests with suspected liver failure	No follow-up required

CB, chronic bronchitis; COPD, chronic obstructive pulmonary disease.

[a] Hypersensitivity is not listed by the FDA. However, it is listed by CIMA/AEMPS.

[b] In a drug interaction study with an oral contraceptive containing gestodene and ethinylestradiol, the overall PDE4 inhibitory activity went up by 17%.

(≥ 97%), and have a high volume of distribution, which is indicative of significant tissue penetration. No dose titration is required for geriatric age, or in cases of kidney disease. The clinical data available on roflumilast in patients with class A mild liver failure according to the Child-Pugh scale are not enough to recommend dose titration. Therefore, roflumilast should be used with caution in these individuals, and is contraindicated in moderate or severe liver failure.[23] Roflumilast N-oxide is nearly 10 times more active than the original drug. The plasma half-life of roflumilast and its active metabolite is 17 to 30 hours, respectively.[24] Its excretion is mostly renal. While its pharmacokinetics is not affected by food intake, it could be affected by drugs that inhibit or induce CYP1A2 and CYP3A4, such as erythromycin, fluconazole, clarithromycin, or rifampicin.[25,26] Contraception is advised in fertile women, avoiding contraceptives with gestodene and ethinylestradiol due to shared metabolism.[25,26]

The pharmacokinetics of 0.3% topical roflumilast cream is similar to that of oral roflumilast, taking into consideration the possibility of systemic absorption. Topically, its bioavailability is nearly 1.5%. After applying 3-to-6.5 grams/day for 15 days, it showed a mean exposure of 72.7 ± 53.1 and 628 ± 648 hours ng/mL.[7,27]

Mechanism of action and pharmacodynamics

The exact mechanism of action of roflumilast is still to be elucidated (figure 2). Roflumilast and its active metabolite, roflumilast N-oxide, are PDE4 inhibitors (PDE4i), which happen to be the main enzymes involved in the metabolism of cyclic adenosine monophosphate (cAMP) found in lung tissue, skin, heart, kidneys, GI tract, and nervous system.[28] At cellular level, PDE4 turns cAMP into adenosine monophosphate (AMP), thereby terminating the cellular messaging started by cAMP.[29] Roflumilast blocks the effect of PDE4, thus leading to the accumulation of cAMP in target cells, and increasing the signaling mediated by this molecule. This results in the inhibition of chemotaxis, reduction of inflammatory infiltration, decreased release of inflammatory and cytotoxic mediators, and an overal reduction of inflammation.[30] In dermatology, PDE4 is present in epidermal keratinocytes, neutrophils, Langerhans cells, and T lymphocytes.[31] Additionally, high levels of PDE4 have been found in peripheral blood mononuclear cells of patients with psoriasis, along with changes to ATP signaling.[32] The effectiveness of roflumilast is based on the inhibition of multiple inflammatory pathways, acting at epidermal level in keratinocytes and Langerhans cells, and dermal level in neutrophils, T lymphocytes, and macrophages.[30,33] In atopic dermatitis, the hyperactivation of PDE4 induces an inflammatory response with polarization towards the Th2 pathway.[31,33] Specifically, cAMP has immunosuppressive and anti-inflammatory properties, which are mostly mediated by the nuclear factor-κB, which is key for the activity of multiple cytokines, including tumor necrosis factor-alpha (TNF-α) and interleukins (IL) 1, 2, 8, 12, 18, 23, 27, or 36.[34,35] The multiple PDE4-mediate signaling pathways suggest that its blockade may be useful to trest various dermatoses, such as hidradenitis suppurativa, recurrent aphthous stomatitis, or lichen planus.[3]

Safety profile

Overall, roflumilast is well-tolerated and has an excellent safety profile[24] (table 3). In clinical trials (CT) on roflumilast to treat COPD and chronic bronchitis, the most common adverse event (AE) reported were diarrhea (8% to 9%), weight loss (6% to 12%), and nausea (5%). The incidence of nasopharyngitis (5% to 8%) and upper respiratory tract infections (4%) has been reported. However, these data are similar to those from the placebo group. AEs were mainly reported within the first weeks of treatment and were mostly self-limiting.[28] A meta-analysis reported a higher rate of AEs in the roflumilast 500 μg/day group vs placebo.[36] A total of 15% discontinued treatment due to AEs (compared to 9% from the placebo group). The most common reasons for drug discontinuation were diarrhea and nausea.[28] These initial analyses also reported higher rates of acute pancreatitis, psychiatric symptoms, and even prostate, lung, and colorectal cancer.[37] However, these initial findings could not be confirmed later, and roflumilast has even been proposed as an adjuvant therapy to treat various neoplasms, such as lung cancer or diffuse large B-cell lymphoma.[38,39]

Regarding weight loss, its incidence was nearly double (67.4% vs 37.7%) in the roflumilast group, and weight loss turned out to be significant (> 10% compared to baseline in 7.1% of the treatment group vs 1.9% of the control group).[37] This significant weight loss was associated with an improved glycemic metabolic profile and constitutes a potential therapeutic approach for the management of obesity, insulin resistance, and metabolic syndrome.[40,41] The psychiatric symptoms included in the initial studies were anxiety, depression, and insomnia.[28] However, subsequent studies have confirmed that this risk is minimal, and in fact, roflumilast could be a promising drug to treat cognitive impairment, Alzheimer's disease, or schizophrenia.[8,10,42] Finally, the increased incidence of atrial fibrillation in patients on oral roflumilast has been a matter of discussion due to its higher incidence rate in the oral roflumilast group (n = 24) compared to the placebo group (n = 9) in pre-commercialization trials. However, this has not been confirmed in the routine clinical practice. Additionally, the results of 24-hour Holter EKG monitoring in 55 patients showed no inter-gropu differences regarding heart rate or the occurrence of arrhythmias.[43]

Long-term safety data with PDE4i, specifically roflumilast, are equally favorable, with no new AEs or cumulative AEs being reported.[44,45] AEs have not been described either in diseases in which this drug is commonly used, such as COPD.[46] Currently, there is an ongoing clinical trial to assess the long-term safety profile of oral roflumilast to treat COPD.[47]

The safety profile of topical roflumilast cream is also favorable, with exceptionally rare serious AE being reported due to its minimal absorption (bioavailability of 1% to 2%). The most common AEs reported include diarrhea (3% to 4%) and headache (2% to 4%), followed by insomnia, nausea, itching, or discomfort at the application site.[7,27]

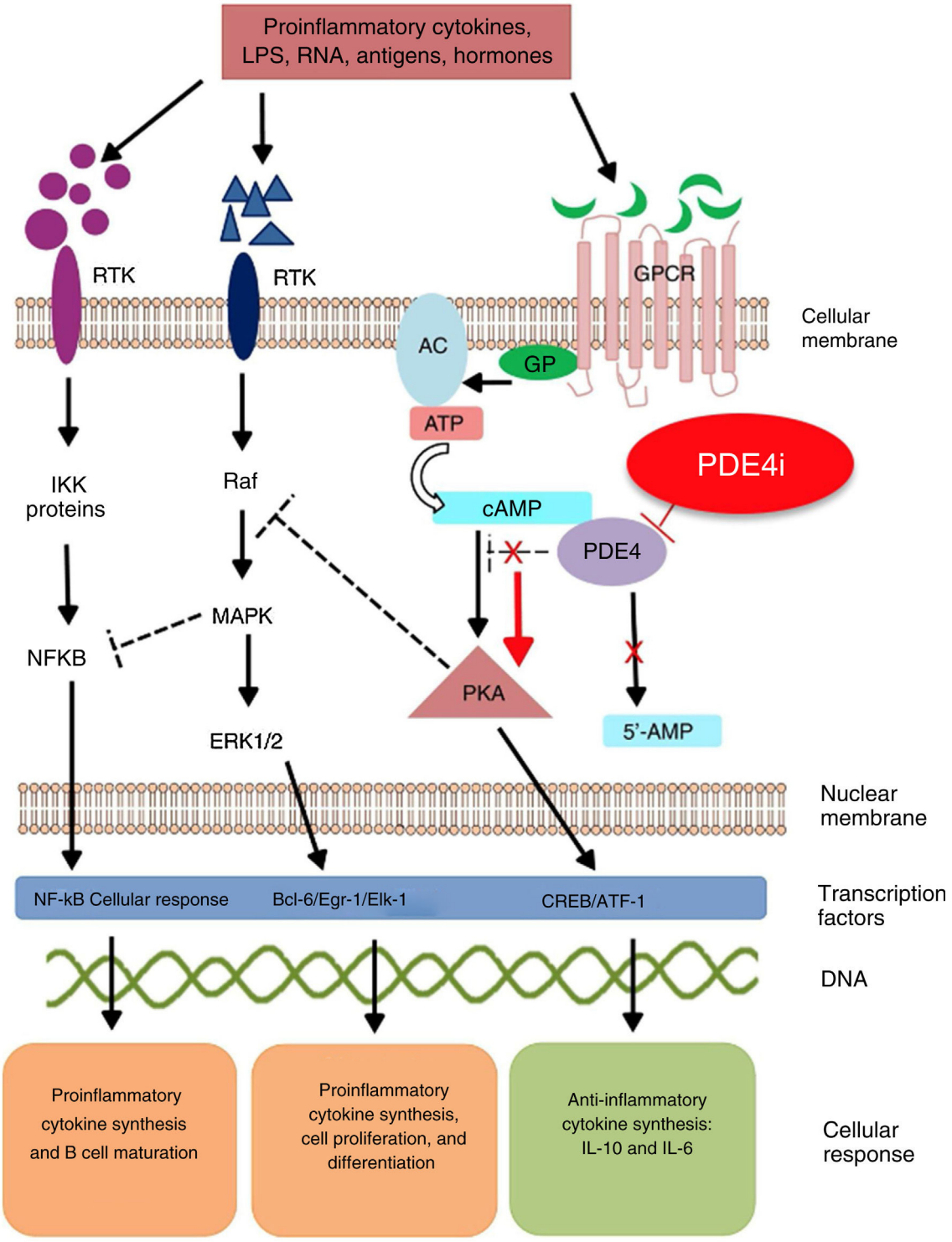

Figure 2 Mechanism of action of roflumilast. Phosphodiesterase inhibitors lead to an accumulation of intracellular cAMP by interfering with its degradation. The increased intracellular concentration of cAMP results in the inhibition of chemotaxis, reduced inflammatory cell infiltration, and decreased release of inflammatory and cytotoxic mediators, thereby reducing inflammation.
5'-AMP, 5'-adenylic acid; AC, adenylate cyclase; ATF, activating transcription factor 1; ATP, adenosine triphosphate; Bcl-6, B-cell lymphoma protein 6; c-AMP, cyclic adenosine monophosphate; CREB, cAMP responsive element; Egr-1, early growth response protein 1; Elk-1, E-26-like protein 1; ERK, extracellular signal-regulated kinase; GP, G protein; GPCR, G protein-coupled receptors; IKKbeta, inhibitor of nuclear factor kappa-B kinase subunit beta; IPDE-4, inhibitor of phosphodiesterase type 4; MAPK, mitogen-activated protein kinases; NFKB, nuclear factor KB; PDE4, phosphodiesterase type 4; PDE4i, phosphodiesterase type 4 inhibitor; PKA, protein kinase A; Raf, rapidly accelerated fibrosarcoma protein kinases; RTK, receptor tyrosine kinases.[34]

Table 3 Adverse events associated with the use of roflumilast.

Frequency	Common (≥ 1/100 to < 1/10)		Uncommon (≥ 1/1000 to < 1/100)		Rare (≥ 1/10 000 to < 1/1000)	
Organ classification	Oral roflumilast	Topical roflumilast	Oral roflumilast	Topical roflumilast	Oral roflumilast	Topical roflumilast
Immune system disorders	—	—	Hypersensitivity	Hypersensitivity	Hives and angioderma	Hives and angioderma
Endocrine disorders	—	—	—	—	Gynecomastia	—
Metabolism and nutrition disorders	Weight loss Decreased appetite	—	—	Weight decrease Decreased appetite	—	—
Psychiatric disorders	Insomnia	—	Anxiety Insomnia	Insomnia	Suicidal ideation and behavior,[a] depression, nervousness, panic attacks	—
Nervous system disorders	Headache	Headache	Tremor Vertigo Dizziness	Tremor Vertigo Dizziness	Dysgeusia	—
Cardiac disorders	—	—	Palpitations	—	—	—
Respiratory, thoracic, and mediastinal disorders	—	—	—	—	Respiratory tract infections (excluding pneumonia)	Respiratory tract infections (excluding pneumonia)
Urinary tract disorders	—	—	—	—	Urinary tract infections	Urinary tract infections
GI disorders	Diarrhea, nausea, abdominal pain	Diarrhea, nausea, abdominal pain	Gastritis, vomiting, gastroesophageal reflux, dyspepsia	—	Hematochezia, constipation	—
Hepatobiliary disorders	—	—	—	—	Elevated GGT and AST levels	—
Skin and subcutaneous tissue disorders	—	Burning at the application site	Nonspecific maculopapular rash	Pain at the application site	Hives and angioedema	Hives and angioedema
Musculoskeletal and connective tissue disorders	—	—	Muscle spasms and weakness, myalgia, back pain	—	Elevated CPK levels	—
General disorders and changes to the administration site	—	—	Malaise, asthenia, fatigue	—	—	—

—: Not described or anecdotal reports; AST, aspartate aminotransferase; CPK, creatine phosphokinase; GGT, gamma-glutamyltransferase.
[a] In clinical trials and post-marketing surveillance, rare cases of suicidal ideation and behavior, including suicide, have been reported.[37,43]

Approved indications in dermatology

The use of oral roflumilast has been approved by the FDA (unlike the EMA) for the topical treatment of plaque psoriasis and mild-to-moderate seborrheic dermatitis.[6,7,27] The first report on roflumilast in the management of plaque psoriasis dates back to 2017 when Michels et al.[48] described a case of psoriasis and concomitant COPD in which skin lesions improved while lung disease was being treated with oral roflumilast. In 2020, Papp et al.[49] reported the first stage I/IIa clinical trial (CT). This trial confirmed that a response was achieved when plaque psoriasis was treated with 0.5% and 0.15% topical roflumilast cream, which was superior compared to the administration of placebo. The DERMIS-1 and DERMIS-2 trials[27] led to the FDA approval of 0.3% topical roflumilast to treat plaque psoriasis, with 42.4% of cases achieving the Investigator's Global Assessment Scale (IGA) endpoint of complete clearance or improved IGA ≥ 2 points compared to baseline vs 6.1% of the patients from the control group (DERMIS-1), and 37.5% achieving the IGA endpoint

Table 4 Studies on topical roflumilast to treat plaque psoriasis and seborrheic dermatitis.[6,7,27,49,50,78,79,82]

Dermatosis	Year, authors	N	Type of study	Study endpoints	Results
Plaque psoriasis	2023, Kircik L et al.[6]	304	Stage IIb randomized clinical trial	Assess the efficacy and safety profile of an 8-week course of 0.3% topical roflumilast vs placebo to treat plaque psoriasis on the body and scalp.	A significantly larger number of patients treated with roflumilast (59.1%) compared to patients treated with the vehicle (11.4%) achieved the IGA endpoint on the scalp on week 8 ($P < .0001$). There was also a significant improvement in secondary endpoints, including body IGA, scalp itch scale, and PSSI.
	2023, Thurston Jr et al.[82]	Review of 495 patients	Post-trial study	Post-trial study of several stage II clinical trials that assessed the pharmacokinetic characteristics of topical 0.3% roflumilast to treat plaque psoriasis	Systemic bioavailability of 1.5%. Skin concentration 61 to 126 times higher compared to oral administration. Roflumilast N-oxide action 8 times higher compared to roflumilast. This effect, however, has not been reported with the topical formulation. Half-life of 4 days
	2022, Stein Gold L et al.[50]	331	Stage IIb randomized clinical trial	Evaluation of itching in patients with plaque psoriasis after a 12-week course of 0.3%, 0.15% topical roflumilast and placebo	0.3% topical roflumilast worked better treating itching and night-time relief compared to 0.15% topical roflumilast and placebo.
	2022, Pixley J et al.[78]	Review of 2064 patients	SR	It included several stage III clinical trials on the effectiveness of topical roflumilast to treat plaque psoriasis	0.3% topical roflumilast is an effective and safe drug to treat plaque and intertriginous psoriasis
	2022, Arcutis biotherapeutics clinical trial[79]	332	Stage III randomized clinical trial	Efficacy and safety profile of a 52-week course of 0.3% topical roflumilast vs vehicle control to treat plaque and intertriginous psoriasis	45% of the topical roflumilast group achieved the IGA endpoint (improvement $\geq$ 2 points compared to baseline) vs 6.1% of the control group
	2022, Lebwohl MG et al.[27]	439 (DERMIS-1 trial) and 442 (DERMIS 2 trial)	Stage III randomized clinical trials	Efficacy and safety profile of an 8-week course of 0.3% topical roflumilast vs vehicle to treat plaque intertriginous psoriasis	42.4% of the patients from the group on topical roflumilast achieved the IGA endpoint compared to 6.1% of the control group (DERMIS-1), and the efficacy of topical roflumilast reached 37.5% in the IGA endpoint (improvement $\geq$ 2 scores from baseline) compared to 6.9% from the control group (DERMIS-2).

Table 4 (*Continued*)

Dermatosis	Year, authors	N	Type of study	Study endpoints	Results
	2020, Papp A et al.[49]	97	Stage I randomized clinical trial (safety)/IIa (dose)	Assess the efficacy and safety profile of a 4-week course of 0.5% topical roflumilast vs 0.15% placebo to treat plaque psoriasis	The primary endpoint (plaque clearance) was achieved in 66% and 67% of the patients from the 0.5% and 0.15% roflumilast groups, respectively, compared to 35% from the placebo group. No differences were reported regarding side effects.
Seborrheic dermatitis	2023, Zirwas MJ et al.[7]	226	Stage IIa randomized clinical trial	Efficacy and safety profile of an 8-week course of 0.3% topical roflumilast vs placebo to treat mild-to-moderate seborrheic dermatitis	Perfil de seguridad adecuado Efficacy and safety profile of an 8-week course of 0.3% topical roflumilast vs placebo to treat mild-to-moderate seborrheic dermatitis. Proper safety profile

COPD, chronic obstructive pulmonary disease; IGA, Investigator's Global Assessment Scale; PSSI, Psoriasis Scalp Severity Index; SR, systematic review.

compared to 6.9% from the control group (DERMIS-2). The safety profile was favorable in both studies, being GI discomfort the most common AE of all.[77] Recently, 2 stage IIb[50] and stage III[6] trials have been published confirming the efficacy profile of 0.3% topical roflumilast to treat pruritus, nocturnal rest, and scalp involvement, respectively (table 4).

The FDA approval of topical roflumilast to treat seborrheic dermatitis was granted back in April 2023, following the publication of the results from a multicenter, placebo-controlled stage IIa CT on the efficacy and safety profile of 0.3% roflumilast in 226 patients with a > 3-month history of seborrheic dermatitis and IGA scores ≥ 3 (≥ moderate) with involvement of < 20% of the body surface area, including the scalp, face, trunk, and intertriginous areas.[7] The trial achieved the target IGA (≥ 2-point clearance from baseline) in 73.8% of the patients on roflumilast, compared to 40.9% of the patients from the control group (P < .001). The difference was significant from the 2nd week of treatment. No higher rate of AEs was ever reported in the roflumilast group compared to the control one.

Off-label use of roflumilast in dermatology

The medical literature available includes various trials (most of them small series of cases or initial CT) on the off-label use of roflumilast in dermatology (table 5). Specifically, we found 4 clinical trials on the use of topical roflumilast. Regarding atopic dermatitis, one stage IIa CT (n = 40) failed to achieve its proposed endpoints with 0.5% topical roflumilast being compared to placebo at 16 weeks. The primary endpoint of this trial was to determine the number of patients who achieved a reduction of, at least, 75% in the Hand Eczema Severity Index (HECSI75) after treatment with roflumilast topical cream.[51] Another randomized stage IIa clinical trial (n = 136) showed an improved Eczema Area and Severity Index (EASI) score at 12 weeks with 0.15% topical roflumilast (superior to that obtained with the 0.05% concentration and placebo). However, these results did not reach statistical significance.[52] Two currently ongoing clinical trials on the effects of topical roflumilast to treat chronic hand eczema,[53] and papulopustular rosacea.[54] The CT on chronic hand eczema (n = 230) is stage IIa trial on the efficacy and safety profile of topical roflumilast cream at 0.3% vs 0.1% vs placebo. The trial will be assessed at week 12. The CT on papulopustular rosacea (n = 40) has already been completed and is currently pending publication. It evaluates the efficacy profile of 0.5% topical roflumilast vs placebo. Recently, a preclinical trial found higher levels of PDE4 in the skin of patients with vitiligo. After the application of topical roflumilast, the PDE4 levels dropped, and skin lesions improved partially.[55]

Regarding the off-label use of oral roflumilast, we found 4 trials on the off-labe use of roflumilast to treat psoriasis (table 5). Gyldenløve et al. have recently reported the efficacy of 500 μg/day of oral roflumilast to treat plaque psoriasis in a stage III CT (n = 46) vs placebo, with 35% of the intervention group achieving PASI 75 vs 13% of the placebo group (P = .014) at week 12. Mostly mild AEs were reported.[45] Recently, the same group published the results of oral roflumilast in the first patient with refractory plaque psoriasis in whom this drug was ever prescribed, a 48-year-old man.[56] They later reported on the long-term disease progression (18 months) of this individual.[57] Recently, its utility has also been described in another clinical case: a 59-year-old man who was simultaneously being treated for COPD and psoriasis.[48] In both cases, roflumilast was used at a dose of 500 μg/day, with no significant adverse events being reported. Aside from psoriasis, the scientific medical literature currently available includes 5 articles on oral roflumilast in dermatological disease (table 5): 1 case series and 4 isolated clinical cases, most of them reported by the same health care center in Denmark. Ring et al. described 1 case of refractory hidradenitis suppurativa with axillary involvement, failed adalimumab and infliximab, and good clinical response to roflumilast at 12 weeks, with associated

Table 5 Clinical trials on the off-label use of roflumilast in dermatology.[45,48,51-54,56-63]

Dermatosis	Year, authors	N	Type of study	Study endpoints	Results
Psoriasis	2023, Gyldenløve M et al.[45]	46	Stage III randomized clinical trial NCT04549870	Assess the efficacy and safety profile profile of oral roflumilast to treat plaque psoriasis	At week 12, 35% of the patients achieved PASI 75 vs 13% from the placebo group ($P = .014$). Two patients required discontinuation due to roflumilast-related adverse events being diarrhea the most common adverse event of all.
Psoriasis	2021, Egeberg A et al.[56]	1	Case report	48-year-old man with plaque psoriasis treated with oral roflumilast 500 μg/day	Complete clearance of lesions after 24 weeks on therapy. No adverse events reported.
Psoriasis	2023, Gyldenløve M et al.[57]	1	Case report	Assess the long-term efficacy and safety profile of oral roflumilast in the patient from the former study[56]	After 18 months of treatment, the patient maintained PASI 0 and had no notable adverse events.
Psoriasis	2017, Michels K et al.[48]	1	Case report	59-year-old man with COPD and erythrodermic psoriasis successfully treated with oral roflumilast 500 μg/day	Improvement in psoriasis occurred incidentally after COPD treatment.
HS	2022, Ring et al.[58]	1	Case report	Assess the response to oral roflumilast in a patient with severe axillary HS on failed adalimumab and infliximab therapy	Adequate response with fewer lesions reported, and no notable adverse events at 3 months. Associated with a 9 kg weight loss.
Recurrent oral aphthosis	2022, Gyldenløve et al.[59]	2	Case series	Assess the response to oral roflumilast in 2 patients with recurrent oral aphthosis who did not meet Behçet's disease criteria	Complete lesion resolution occurred early (2 to 3 weeks) and was sustained after 3 months of treatment. Good safety profile.
Behçet's disease	2023, Peñuelas et al.[62]	1	Case report	Assess the response to oral roflumilast 250 μg/day in a patient with refractory Behçet's disease	Favorable response to roflumilast therapy without noticeable adverse events.
Nummular eczema	2022, Gyldenløve et al.[60]	1	Case report	Assess the response to oral roflumilast 500 μg/day in a 69-year-old patient with nummular eczema refractory to topical steroids, UVB, methotrexate, and azathioprine	Early response (2 weeks) and complete lesion clearance after 3 months of treatment. Good safety profile.
Erosive lichen planus	2023, Fage et al.[61]	1	Case report	Assess the response to oral roflumilast in a patient with erosive oral lichen planus refractory to topical and oral steroids, methotrexate, cyclosporine, azathioprine, apremilast, and adalimumab	Substantial resolution of lesions after 3 months of treatment, initially concomitant with descending prednisone (7.5 mg to 2.5 mg after 3 months on roflumilast).
Atopic dermatitis	Clinical trial[51]	40	Stage IIa clinical trial NCT01856764	Assess the efficacy and safety profile of 0.5% topical roflumilast vs placebo to treat atopic dermatitis	No superior results were achieved compared to placebo in the roflumilast group.

Table 5 (*Continued*)

Dermatosis	Year, authors	N	Type of study	Study endpoints	Results
Atopic dermatitis	Clinical trial[52]	136	Stage IIa clinical trial NCT04773587	Assess the efficacy and safety profile of 0.15% topical roflumilast vs 0.05% topical roflumilast vs placebo to treat atopic dermatitis	A decrease in EASI of 6.4 points in the 0.15% roflumilast group, 6 points in the 0.05% roflumilast group, and 4.8 points in the control group, without statistical significance. Good safety profile.
Chronic hand eczema	Clinical trial[63]	40	Stage IV clinical trial (Recruitment in progress) NCT05682859	Assess the efficacy and safety profile of oral roflumilast vs placebo to treat chronic hand eczema	Results pending publication
Chronic hand eczema	Clinical trial[53]	230	Completed stage IIa clinical trial NCT04378569	Assess the efficacy and safety profile of 0.3% vs 0.1% topical roflumilast vs placebo to treat chronic hand eczema	Results pending publication
Rosacea	Clinical trial[54]	40	Completed stage II clinical trial (Results pending publication) NCT05278624	Assess the efficacy and safety profile of 0.5% topical roflumilast vs placebo to treat papulopustular rosacea	Results pending publication

HS, hidradenitis suppurativa; UVB, ultraviolet-B Radiation therapy.

weight loss.[58] Gyldenløve et al. reported 2 cases of recurrent oral aphthosis treated with oral roflumilast 500 μg/day, showing proper and rapid responses within 2 to 3 weeks and maintained responses after 3 months of treatment.[59] Similarly, they also described 1 case of nummular eczema with failed multiple treatments that, somehow, achieved an early and sustained response to oral roflumilast, without visible adverse events being reported.[60] There was also 1 case of erosive oral lichen planus refractory to first-line therapies and on systemic corticosteroids. Oral roflumilast allowed for down-titration of prednisone to 2.5 mg/day at 3 months.[61] A Spanish group recently reported 1 case of refractory Behçet's disease successfully treated with roflumilast 250 μg/day, without significant adverse events being reported.[62] Finally, a stage IV clinical trial (n = 40) currently in the recruitment stage is evaluating oral roflumilast at a dose of 500 μg/day vs placebo to treat chronic hand eczema.[63]

Dermatoses that could potentially benefit from roflumilast

Given its mechanism of action, which is similar to that of apremilast and the possibility of elevated PDE4 levels, multiple dermatoses in which this drug has been used off-label could potentially benefit from oral or topical roflumilast (table 6). Among these we find primarily autoimmune dermatoses like vitiligo or alopecia areata,[3] erythematosquamous diseases similar to psoriasis such as pityriasis rubra pilaris,[64] or Sneddon-Wilkinson syndrome,[65] blistering diseases such as vulgar pemphigus or acquired epidermolysis bullosa,[3] genodermatoses such as familial benign pemphigus (Hailey-Hailey disease),[66] or ichthyosis.[3] Other diseases where apremilast could also be useful include hidradenitis suppurativa,[67] cutaneous lichen planus,[68] or other lichenoid and interface dermatitis,[69] cutaneous lupus erythematosus[70], or cutaneous sarcoidosis.[71] Its potential application in morphea, a relatively common disease where PDE4i have shown to reduce dermal fibrosis is of special interest. In fact, good results have been reported with apremilast to treat this entity.[72–74]

Discussion

The management of moderate-to-severe inflammatory dermatoses often requires the use of immunomodulators or immunosuppressants, which are often used off-label in dermatology. Despite the addition of small molecules and biologic agents to our therapeutic arsenal, there is a need for new cost-effective immunomodulatory therapies with a good safety profile.[75–77] One significant advantage of roflumilast is that it is not expensive (nearly €30/month in Spain for the oral formulation of 500 μg/day, which is similar to the price reported in other countries).[59] In fact, its price is lower than that of classic immunosuppressants such as oral cyclosporine or subcutaneous methotrexate. Another

Table 6 Off-label use of apremilast and potential uses of roflumilast in dermatology.

Alopecia areata[3]	Frontal fibrosing alopecia[3]
Central centrifugal cicatricial alopecia[3]	Chronic actinic dermatitis[3]
Lichenoid interface dermatitis[69]	Atopic dermatitis[3]
Refractory seborrheic dermatitis[3]	Chronic hand eczema[3]
Nummular eczema[3]	Behçet's disease[3]
Acquired epidermolysis bullosa[3]	Perforating diseases[3]
Erythema annulare centrifugum[3]	Recurrent erythema multiforme[3]
Leprous nodular erythema[3]	Recurrent aphthous stomatitis[3]
Decalvans folliculitis[3]	Granuloma annulare[3]
Orofacial granulomatosis[3]	Hidradenitis suppurativa[67]
Lamellar ichthyosis[3]	Dermatomyositis skin lesions[3]
Lichen planus[68]	Mucosal lichen planus[3]
Lichen planopilaris[3]	Discoid cutaneous lupus erythematosus[70]
Morphea[72–74]	Pyoderma gangrenosum[3]
P-2003 pemphigoid[3]	Pityriasis rubra pilaris[64]
Nodular prurigo[3]	Palmoplantar pustulosis[3]
Palmoplantar keratoderma[3]	Rosacea[3]
Sarcoidosis[71]	Sneddon-Wilkinson syndrome[65]
SAPHO syndrome[3]	Vitiligo[3]
Vulgar pemphigus[3]	Benign familial pemphigus[66]
Oral ulcers[3]	

SAPHO, synovitis acne pustulosis hyperostosis osteitis.

advantage is its excellent safety profile, with few contraindications and mostly GI AEs, which is very similar to what has already been reported with apremilast. Regarding serious AEs, a still-to-be elucidated relationship has been suggested on the use of roflumilast and atrial fibrillation. The association between roflumilast and suicide is also controversial and has not been found in subsequent studies.[37,43] This drug has been on the market for over 10 years. During this time no new AEs or deleterious cumulative effects have ever been reported from its long-term use.[44,45] However, GI AEs can be very bothersome and lead to its discontinuation in a significant number of patients. Therefore, proper titration is essential, with gradual up-titration. Overall, it is recommended to start at a dose of 250 μg/day with or without food and always at the same time of day. With proper responses and in the absence of significant AEs, up-titrating to the optimal dose of 500 μg/day is advised. Its use has been tested for up to 1 year, although it may be continued for longer periods of time at the physician's discretion.[23]

Convenient dosing and the possibility of dual application, both topically and orally are among the advantages of roflumilast.[78] Additionally, it may lead to weight loss associated with an improved metabolic profile and insulin resistance, which makes it a perfect option for patients with dermatoses and overweight, such as those with hidradenitis suppurativa.[58] However, this needs to be demonstrated in prospective studies with proper follow-up.

Regarding its topical use, roflumilast should be applied once a day, with a small layer being applied to the affected skin. It is not yet available in Spain.

Its application in dermatology parallels former studies on apremilast, another PDE4i with a similar affinity to PDE4 and no higher frequency of side events. However, to date, no studies have compared the side effect profiles of apremilast and roflumilast.[79] In our review, we found that roflumilast has been used off-label in its oral form to treat various dermatoses (table 5), including psoriasis, hidradenitis suppurativa,[58] recurrent oral aphthosis,[59] Behçet's disease,[62] erosive oral lichen planus,[61] and nummular eczema,[60] among others. Also, its pharmacokinetic and pharmacodynamic analogy to apremilast allows us to hypothesize that it could be useful to treat multiple skin diseases. However, the evidence available to date is still limited and recommendations on this regard cannot be made yet. In the coming years, new indications for oral or topical roflumilast in dermatology may be approved, and dermatologists still need to become familiar with this promising drug.

Limitations

This review has the limitation of being narrative and not a systematic review or meta-analysis. Additionally, many of the studies included, especially those on off-label uses of roflumilast, are case series, have small sample sizes, or a retrospective design. Additionally, its potential uses have been extrapolated from apremilast due to pharmacokinetic and pharmacodynamic analogies. All these factors make it difficult to generalize the findings reported and draw definitive conclusions.

Conclusions

Roflumilast is a drug that has been approved in dermatology to treat plaque psoriasis and mild-to-moderate seborrheic dermatitis, both in topical formulations. There are reports and studies available, most small, which support the utility of oral roflumilast to treat psoriasis, hidradenitis suppurativa, recurrent oral aphthosis, nummular eczema, and lichen

planus, among others. It has a very favorable safety profile, is cost-effective, and is widely available. New controlled studies are needed to assess its efficacy profile in inflammatory dermatoses and establish new approved indications for this promising molecule.

Conflicts of interest

None declared.

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