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On- and Off-Label Uses of Apremilast in Dermatology

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ABSTRACT Apremilast is an oral small-molecule phosphodiesterase 4 inhibitor with a multilevel immunomodulating mechanism of action. It has received approval in many countries for the use in moderate-to-severe plaque psoriasis and active psoriatic arthritis in adults. Herein, we review the literature concerning the use of apremilast in dermatology, with a focus on both the on- and the off-label uses of this medication in dermatologic conditions. This paper is a systematic overview of all the reported uses of apremilast in dermatology described in the literature so far and was conducted according to the PRISMA Guidelines for systematic reviews. There are several original articles, case series and case reports In the literature that present either encouraging or less promising results concerning the efficacy and safety of apremilast in numerous inflammatory dermatological diseases. Despite the potential effectiveness of apremilast in various indications, however, randomized clinical trials on larger patient cohorts and with long-term follow-up are necessary in order to adequately establish the role of apremilast in dermatology overall.

KEY WORDS: apremilast, dermatology, indications

INTRODUCTION

Apremilast (Otezla®, Celgene Distribution B.V. Winthontlaan 6 N 3526 KV Utrecht Netherlands) is a small molecule that acts as an inhibitor of phosphodiesterase 4 (PDE4) and is orally administered (1). Intracellular cAMP is elevated through the inhibition of PDE-4, leading to a downregulation of the inflammatory response and an upregulation of anti-inflammatory cytokines (1, 2). It was first approved by the United States Food and Drug Administration (FDA) in 2014 for treatment of adults with active psoriatic arthritis and moderate-to-severe chronic plaque psoriasis (2). Due to its immunoregulatory –rather than immunosuppressive – properties as well as its excellent safety profile, apremilast has been given consideration as a potential therapeutic alternative option for other inflammatory conditions as well, such as Behcet's disease or hidradenitis suppurativa, though just as an off-label option since no official approval for these conditions has yet been licensed (2,3). The term "off-label" refers to the use of a medication for a disease in an administration route or in a patient population that is not stated officially in the product characteristics summary of the given drug, but this however does not necessarily imply its illegal use (4). The off-label use of various medications is a phenomenon commonly seen in daily medical practice, and has on several occasions opened the way for the release of official commercial licenses, such as in the case of omalizumab and chronic urticaria (5). Herein we review the reported on- and off-label uses of apremilast in the spectrum of dermatologic diseases over the past years. To our knowledge, this is the first report summarizing the reported off-label uses of apremilast for dermatologic conditions

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PATIENTS AND METHODS

This study was conducted according to the PRISMA guidelines (Preferred Reporting Items for Systematic Reviews) for systematic reviews. The databases MEDLINE (PubMed), SCOPUS, and EMBASE were thoroughly searched using the following Mesh key terms: "apremilast" or "Otezla®" AND "therapy", "treatment", "management", "use", "off-label". Further papers were also identified from the reference lists of the above retrieved papers and citations. Our search included articles in the English language published between 2003 and 2019. The selection process included first screening the titles and abstracts and then evaluation of full text articles.

RESULTS AND DISCUSSION

I. On-label use of apremilast

i. Moderate-to-severe plaque psoriasis in adults

The safety and efficacy of apremilast for the treatment of moderate-to-severe plaque psoriasis in adults has been documented in several phase II and phase III clinical trials (3,6-9). In the ESTEEM-1 and -2 phase III studies, apremilast 30 mg twice daily was demonstrated to be of superior efficacy compared with placebo, with a PASI75 (Psoriasis Area and Severity Index) response at week 16 of 33% vs 5% and 29% vs 6%, respectively (6,7). The time of loss of response after re-randomization to placebo varied from 5.1 to 12.4 weeks among the two studies (3,6,7). The phase IIIb of the multinational double-blind randomized LIBERATE study demonstrated PASI75 response rates at week 16 of 39.8% for apremilast 30 mg BID (Bis In Die), 48.2% for etanercept, and 11.9% for placebo, while at week 52, after already having switched all the placebo and etanercept patients at week 16 to apremilast, the PASI75 response rates were calculated as 47.9 for the placebo-to-apremilast group, 49.4% for the etanercept-to-apremilast group, and 47.3% for the apremilast group (1,8). Finally, the efficacy of apremilast versus placebo was also demonstrated in the phase IV double-blind, randomized, placebo-controlled, multicenter UNVEIL study: here systemic- and biologic-naive adult patients with moderate psoriasis (BSA 5-10%) were randomized (2:1) to receive apremilast 30 mg BID or placebo, initially for 16 weeks. At week 16, the apremilast group remained on the same therapy up to week 52, while the placebo group switched to apremilast (open-label apremilast treatment phase). The efficacy was assessed using the product of PGA (Physician Global Assessment) and BSA (Body Surface Area) (PGA×BSA) and the Dermatology Life Quality Index (DLQI; mean change from baseline) instead of the PASI score (9). At week 52, an improvement of the PGA×BSA scores was seen in both groups, with a reduction from baseline by 55.5% in the apremilast/apremilast group and by 42.2% in the placebo/apremilast group (9). The safety profile of apremilast was comparable among all the above studies, with gastrointestinal side effects in the form of mild diarrhea and nausea documented as the most frequent adverse reactions (1, 7-9).

ii. Active psoriatic arthritis in adults

Apremilast received its first global approval by the FDA on 21 March 2014, for the treatment of active psoriatic arthritis (PsA) in adults (2). The results of four randomized, double-blind, placebo-controlled parallel-group phase III trials, PALACE-1, -2, -3, and -4, demonstrated the efficacy of apremilast 30mg BID or 20 mg BID compared with placebo in systemic-therapy-naïve patients or in patients previously treated with disease-modifying anti-rheumatic drugs (DMARDs) and/or biologics (10-13). In the randomized, double-blind, multinational, phase IIIb ACTIVE trial, apremilast showed both early (at 2 weeks) and sustained improvement of the PsA symptoms: biological-naïve patients were randomized to receive apremilast 30 mg BID or placebo for 24 weeks, however a switch-over to apremilast was possible at week 16 for patients of the placebo group who had not shown an improvement by 10% in swollen joint count (SJC) and tender joint count (TJC) (14). At week 24, all remaining placebo subjects switched over to apremilast 30 mg BID. ACR20 (American College of Rheumatology response criteria, 20% improvement) at week 2 was documented in 16.4 vs 6.4% in the apremilast and placebo group, respectively, implying an early onset of efficacy for apremilast (14). ACR20 at weeks 16 and 24 was significantly higher in the apremilast group, compared with placebo (38.2% vs 20.2% and 43.6% vs 24.8%, respectively) (14). The good clinical response was maintained up to week 52 for all patients (regardless their initial treatment) (14). Regarding the safety profile of apremilast in these patient groups, diarrhea and nausea were the most commonly reported side-effects, with a prevalence similar to studies on plaque psoriasis (3,15). The discontinuation rate due to adverse reactions was remained low across all studies (15).

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II.
Off-label use of apremilast

i.
Psoriasis palmoplantaris (PP) and palmoplantar pustulosis (PPP)

Palmoplantar psoriasis (PP) is a condition that can severely affect patient quality of life and can prove to be refractory to several systemic treatments, including biologics (16,17). Bissonnette *et al.* performed a double-blind, placebo-controlled, randomized study where 100 adult patients with moderate-to-severe PP were randomized to either apremilast 30 mg BID or placebo, initially for 16 weeks. At week 16, all patients in the placebo group switched over to apremilast until week 32 (17). While there was no significant difference in the proportion of patients achieving a PPPGA (Palmoplantar Psoriasis Physician Global Assessment) of 0/1 at week 16 with apremilast (14%) or placebo (4%), there was a significant difference between apremilast and placebo at week 16 for other secondary endpoints, such as change from baseline in PPPASI and PPPGA, proportion of patients achieving a 75% improvement in PPPASI (Palmoplantar Psoriasis Area Severity Index), and change from baseline in DLQI, suggesting a potential use of apremilast as a treatment option for PP (17). Results addressing the therapeutical benefit of apremilast in PP were reported in studies on plaque psoriasis, where a collateral improvement of PP symptoms was documented: a post hoc, pooled analysis of ESTEEM 1, ESTEEM 2, and a phase IIb, multicenter, randomized, placebo-controlled, dose-ranging study demonstrated that a significantly larger proportion of patients with PP receiving apremilast achieved a PPPGA score of 0 (clear) or 1 (almost clear) at week 16, versus the placebo group (48% vs 27%) (18).

Palmoplantar pustulosis (PPP) is an inflammatory bilateral dermatosis that affects the palms and/or soles (19). Whether or not PP and PPP are different variations of the same entity is a debatable issue (19). For many, PPP is clinically distinguished from PP by the absence of other psoriasis signs and by a predilection for histologic involvement of the acrosyringium (19). When it comes to PPP, no large-scale clinical trials have yet been published and the trials and analyses mentioned above did not assess palmoplantar pustules (17,18). The use of apremilast for PPP is reported mainly in case series and case reports: a total of 5 published patients in the literature – one of them as a manifestation of SAPHO syndrome – showed an early improvement under this medication, after several unsuccessful treatments also involving biologic agents (19-22).

ii.
Pustular psoriasis, nail and scalp psoriasis, erythrodermic psoriasis

Pustular psoriasis, either in its generalized form, i.e. the von Zumbusch type, or as acrodermatitis continua of Hallopeau, has not officially received approval as an indication for apremilast use (23). In the literature, there are isolated case reports that demonstrate the quick efficacy of apremilast in the management of this entity, but studies in larger patient cohorts are necessary in order to draw definite conclusions (23-25). In the report by Georgakopoulos *et al.*, apremilast was administered parallel to a treatment with infliximab, leading to a successful remission of a refractory generalized pustular psoriasis, indicating that a combination of this agent with other biologics is a possible therapeutic strategy with an attractive safety- and interactions-profile (24).

The ESTEEM 1 and 2 studies on apremilast versus placebo for moderate-to-severe plaque psoriasis reported the following results from subgroup analyses of patients who presented with nail and scalp psoriasis at baseline: apremilast 30 mg BID led to a significant improvement of both conditions from baseline at week 16 compared with placebo, with a NAPSI (Nail Psoriasis Severity Index) score improvement in ESTEEM 1 by -22.5 vs +6.5% and in ESTEEM 2 -29.0 vs -7.1%, and a significantly higher SPGA (Scalp Physician Global Assessment) response in both ESTEEM 1 and 2 (26). The use of apremilast in nail psoriasis has also been documented in several case series and case reports, where both systemic-therapy-naïve or experienced patients were successfully treated with this agent (27,28). The preparation of an apremilast nail lacquer formulation has been reported by Kushwaha *et al.*, opening the way for potential future use of this medication as a local treatment in nail psoriasis (29).

As far as erythrodermic psoriasis is concerned, only two published reports demonstrate the successful administration of apremilast for this condition, with an initially significant and rapid PASI improvement of the presented patients (30,31). In the first case, however, the therapy had to be discontinued due to apremilast-attributed atrial fibrillation (30), and in the second case the treatment was switched over to biologics after 3-6 months due to failure to maintain the initial good therapeutic result (31).

iii.
Pediatric psoriasis

Since the safety of apremilast has not been established in children, the clinical data are extremely scarce (32). In the only report in the literature, Smith

presented the case of an otherwise healthy 14-year-old patient who showed significant improvement within the first month of a treatment with apremilast 30 mg BID (33). A phase II, multinational, open-label study in subjects with moderate to severe plaque psoriasis aged 6 to 17 years (funded by Celgene; ClinicalTrials.gov Identifier: NCT02576678) is actually ongoing, in order to evaluate the safety, tolerability, and pharmacokinetics of apremilast in the pediatric population (34).

iv. Behcet syndrome and complex refractory aphthosis in the absence of Behcet's disease

The effect of apremilast in several inflammatory pathways suggest that this agent could display a therapeutic benefit in chronic inflammatory conditions, such as Behcet syndrome (35). In a phase II, multicenter, placebo-controlled study, 111 patients with Behcet's syndrome were assessed for the management of oral ulcers under apremilast: apremilast 30 mg BID led to a rapid and significant improvement of the oral lesions and pain as well as an improvement in quality of life compared with the placebo group (mean number of oral ulcers at week 12 by 0.5+/- 1 vs 2.1 +/-2.6, respectively, and mean decline in pain from oral lesions from baseline to week 12 by .44.7±24.3 mm vs -16.0±32.5 mm, as measured using a 100 mm visual analogue scale, with negative values expressing improvement) (35). Apart from this study, further results are expected from an ongoing phase III, randomized, double-blind study in order to assess the efficacy and safety of apremilast in patients with active Behcet's disease (funded by Celgene; ClinicalTrials.gov Identifier: NCT02307513) (36). Finally, other case reports indicate a potential successful use of apremilast in Behcet's syndrome either as monotherapy or in combination with other immunosuppressives (37), or in complex recurrent oral and/or genital aphthosis in the absence of Behcet's disease (38,39).

v. Atopic dermatitis

Regarding the use of apremilast in atopic dermatitis (AD), the results of different studies are generally encouraging, but with slight variations (40-42). In a phase II, double-blind, placebo-controlled trial, 185 patients were assigned either to apremilast 30 mg BID or apremilast 40 mg BID versus placebo up to week 12, with all patients receiving apremilast 30 mg or 40 mg up to week 24 (40). A significant improvement from baseline in Eczema Area and Severity Index (EASI) was observed in patients who received apremilast 40 mg compared with placebo (mean [standard deviation] by -31.6% (44.6 vs -11.0%, respectively) at week 12. Patients on apremilast 30 mg presented with EASI improvement in comparison with placebo at week 12, which was however not statistically significant (40). The subjects who were switched over to apremilast 30 mg or apremilast 40 mg at week 12 presented with EASI improvement at week 24 consistent with the respective initial apremilast groups (40). The safety profile of apremilast was comparable to the studies on psoriasis, with the prevalence of serious adverse events being slightly higher in the apremilast 40 mg group (40). An unexpected elevated occurrence of cellulitis was observed in this study (40). In a smaller, investigator-initiated, open-label pilot study, 16 subjects received apremilast 20 mg BID for three months or 30 mg BID for six months (41). Pruritus and DLQI score were significantly improved in the 20 mg group, while the 30 mg group also showed a significant reduction in EASI score, DLQI, and clinical appearance of the lesions (41). Smaller case series and case reports on isolated patients further indicate the potential role of apremilast in the treatment of recalcitrant AD, as well as its beneficial effect on pruritus and quality of life (43-44).

vi. Other inflammatory dermatologic conditions

The multi-level anti-inflammatory mechanism of action of apremilast and its attractive safety, contraindication, and interaction profile (1-3), as well as its immunomodulating rather than immunosuppressive properties (45) have resulted in its off-label administration, in isolated cases, for several other dermatological conditions where conventional therapies have failed to achieve a good therapeutic outcome (46-66).

a. Pityriasis rubra pilaris

Pityriasis rubra pilaris (PRP) is a chronic inflammatory skin condition characterized by erythema, hyperkeratotic follicular papules, and palmoplantar keratoderma (46,47). So far, 4 patients have been successfully treated with apremilast 30 mg once or twice daily (46-49). Although the exact pathogenetic mechanism of action of apremilast in this case is not fully understood, it is hypothesized that the latter acts through the suppression of CARD-14 and NF-kB in keratinocytes and dermal inflammatory cells (46).

b.
Lichen planus and lichen planus mucosae

The use of apremilast in cases of cutaneous lichen-planus lesions (50) or in cases of lichen planus mucosae, with lesions mostly in the oral cavity (51-53), has also been described. In a small case series by Paul *et al.*, three out of ten patients with cutaneous lichen planus receiving apremilast 20 mg BID daily for 12 weeks showed a 2-grade or more improvement in PGA scores, while all patients achieved an improvement in parameters such as itch, medial lesion count, and DLQI (50). The effect of apremilast in recalcitrant lichen planus mucosae has been reported in three patients so far, with one of them demonstrating significant improvement in lichen-planus mucosae-associated stenotic esophagitis as well (51-53).

c.
Alopecia areata

The data on the efficacy of apremilast in the treatment of alopecia areata are contradictory (54-57). While apremilast has been demonstrated to be effective in treating humanized alopecia areata in mouse models (54), a double-blind placebo-controlled study in 30 patients with moderate-to-severe alopecia areata who were randomized 2:1 to receive apremilast 30 mg BID over a period of 24 weeks failed to demonstrate a statistically significant response in the apremilast versus the placebo group (55). Similar results indicating a lack of efficacy or apremilast in alopecia areata were reported in a small case series of 9 patients by Liu *et al.* (56). Only a case report demonstrating significant scalp hair growth under apremilast 30mg BID over 15 weeks in a woman with alopecia universalis was present in the literature; however, the possibility of a spontaneous remission in this case cannot be ruled out (57).

d.
Hidradenitis suppurativa

Regarding hidradenitis suppurativa, apremilast 30 mg BID for 16 weeks resulted in a clinically significant

Table 1. Use of apremilast in less frequent dermatoses

Dermatosis	Reference	Number of patients	Dosage of apremilast	Time to Improvement	Concomitant medication
Pyoderma gangraenosum	Laird *et al.* (60)	1	30mg BID	Approximately 4 months	Initially oral prednisone and s.c. methotrexate, which could be tapered within 4 to 5 months
Dermatomyositis	Bitar *et al.* (61)	3	30mg BID	Approximately 1 month	Patient 1 and 2: Mycophenolate mofetil and prednisone, which could be discontinued Patient 3: Mycophenolate mofetil, prednisone, hydroxychloroquine. Relapse after 9 months, apremilast was discontinued
Hailey-Hailey Disease	Kieffer *et al.* (62)	4	30mg BID	Approximately 1 month	No concomitant medication
Epidermolysis bullosa simplex	Castela *et al.* (63)	3	30mg BID	Patient 1: 10 days Patient 2: 15 days Patient 3: 30 days	No concomitant medication
Erythema exsudativum multiforme	Chen *et al.* (64)	3	Patient 1 and 2: 30mg BID	Patient 1: 1 week Patient 2: 1 month	No concomitant medication
Vitiligo	Huff *et al.* (65)	1	30mg BID	Approximately 6 weeks	Intermittent administration of 60m IM triamcinolone acetonide
Sarcoidosis	Baughman *et al.* (66)	15	20mg BID	Approximately 4 weeks	Not clearly specified in the study
Discoid lupus erythematodes	De Souza *et al.* [67]	8	20mg BID	Not mentioned in text	Not mentioned in text

improvement with a good short-term safety profile in the apremilast group compared with placebo, in a randomized controlled trial with 20 patients (53.3% versus 0.0%, respectively) (58). Comparable promising results were seen in a small case series of 9 patients by Weber *et al.* (59).

vii. Other less frequent dermatoses

Isolated case reports or small case series report the successful administration of apremilast in less frequent conditions, either as monotherapy or in combination with other immunosuppressive or immunomodulatory medication (60-67). These are summarized in Table 1.

CONCLUSION

Due to its versatile immunomodulating mechanism of action as well as its attractive safety and interaction profile, apremilast offers the possibility of wide-spectrum use in several inflammatory conditions (1-3). A number of studies concerning the off-label uses of apremilast can be found in the literature, describing either a complete or a partial clinical improvement and either long- or short-term efficacy of this medication (60-67). The vast majority of the reports demonstrate a rather favorable adverse-events-profile of apremilast (60-67). Clinical trials in larger patient cohorts and with long-term follow-ups are necessary in order to adequately evaluate the efficacy, tolerability, and appropriate dosing of apremilast in the off-label indications.

Abbreviations:

ACR American College of Rheumatology Response Criteria
AD Atopic Dermatitis
BID Bis In Die
BSA Body Surface Area
DLQI Dermatological Life Quality Index
DMARDs Disease-Modifying Anti-Rheumatic Drugs
EASI Eczema Area and Severity Index
FDA United States Food and Drug Administration
NAPSI Nail Psoriasis Severity Index
PASI Psoriasis Area Severity Index
PDE4 Phosphodiesterase 4
PGA Physician Global Assessment
PP Palmoplantar Psoriasis
PPP Palmoplantar Pustulosis
PPPASI Palmoplantar Psoriasis Area Severity Index
PPPGA Palmoplantar Psoriasis Physician Global Assessment
PRP Pityriasis Rubra Pilaris
PsA Psoriatic Arthritis
SJC Swollen Joint Count
SPGA Scalp Physician Global Assessment
TJC Tender Joint Count

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