Review paper

# Topical proactive therapy in dermatology. A scoping review

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## Abstract

The term 'proactive therapy' refers to a long-term management of clinically intact skin in previously disease-affected areas. This method was initially implemented in atopic dermatitis to maintain the remission and decrease the risk of exacerbations. Proactive therapy aims to limit the need for reactive treatment and improve the patients' quality of life. A proactive approach is likely to be adopted for other relapsing and inflammatory skin conditions in the future. This scoping review aims to identify dermatological conditions to be treated with the proactive approach, evaluate the available evidence for its efficacy and safety, as well as highlight the research gaps.

**Key words:** anti-inflammatory, atopic dermatitis, low-dose, maintenance, proactive therapy, subclinical inflammation.

## Introduction

The term 'proactive therapy' in dermatology is defined as a long-term, minimal-dose, intermittent application of anti-inflammatory topical agents on previously disease-affected skin [1]. This approach was first used in 2008 by Wollenberg *et al.* [2] as an alternative therapeutic strategy for atopic dermatitis (AD). Defining this emerging therapy by Wollenberg *et al.* [2] in a study with tacrolimus was preceded by a few clinical trials reporting successful maintenance of AD remission using topical fluticasone propionate, published subsequently by van der Meer *et al.* [3] in 1999, Hanifin *et al.* [4] in 2002, and Berth-Jones *et al.* [5] in 2003. Over the past two decades, the proactive approach has become a well-established therapy for AD and further adapted for the treatment of other relapsing dermatoses.

The proactive approach can be introduced after active skin lesions have clinically subsided during initial treatment (i.e. 'reactive therapy') [1, 2, 6] using the same topical fixed-dose medication at reduced frequency. Its primary objective is to prolong disease remission by reducing the inflammatory infiltrate in the skin. Subclinical inflammation that contributes to relapses has been identified in biopsy specimens of seemingly intact skin of patients with psoriasis and eczema [7–9]. The principles and safety of long-term drug application must be addressed before starting proactive therapy to prevent lack of adherence, e.g. due to the widely observed corticophobia [10] (Table 1).

The aim of this scoping review is to analyse the well-established and emerging applications of proactive therapy in dermatology [11]. PubMed, Embase, and Web of Science were searched without date restrictions to find eligible human studies in English. Retrospective studies were excluded. PRISMA Extension for Scoping Reviews and PRISMA 2020 guidelines were followed to write this review [12, 13]. Indications, treatment strategies, safety, tolerance, and outcomes of the proactive approach were

**Table 1.** Proactive therapy: advantages and disadvantages

| Advantages | Disadvantages |
|---|---|
| • Good safety profile, including a low risk of side effects | • Requires good compliance |
| • Cost efficiency | • No data regarding long-term (> 52 weeks; disease-dependent) efficacy and safety |
| • Reduced number and decreased severity of exacerbations compared to reactive treatment alone | • No data regarding any delayed adverse events following proactive therapy discontinuation |
| • Improved quality of life compared to reactive treatment alone | |

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**Table 2.** A summary of all available studies of proactive therapy in psoriasis, seborrheic dermatitis, vulvar lichen sclerosus, and condylomata acuminata: detailed information from reported studies

| Dermatologic condition | Authors [year] | Study type | Proactive maintenance scheme | Relapses during follow-up in % of experimental group patients who completed the trial (number of patients); assessment scale used | Number of patients enrolled in the proactive treatment group | Possible drug-related adverse reactions during proactive therapy (number of patients) |
|---|---|---|---|---|---|---|
| Psoriasis | Lebwohl *et al.* (2021) | DB, PC, RCT | 0.005% calcipotriene and betamethasone dipropionate 0.064% foam twice weekly for 52 weeks | 77% (101/131); PGA | 272 | Chorioretinopathy (1), mild application site pain (3) |
| Seborrheic dermatitis | Kim *et al.* (2013) | DB, PC, RCT | 0.1% tacrolimus ointment twice weekly for 10 weeks | 32% (9.4/29); IGA | 32 | Burning (6) and tingling (2) sensations |
| | | | 0.1% tacrolimus ointment once weekly for 10 weeks | 51% (11.4/22); IGA | 28 | Burning (4) and tingling (2) sensations |
| | Joly *et al.* (2021) | DB, RCT | 0.1% tacrolimus ointment twice weekly for 24 weeks | 21% (12/57*); 8-point assessment scale | 57 | Pruritus (23), burning sensation (29), erythema (3), folliculitis (4), herpes (2), conjunctivitis (1) |
| | | | 1% ciclopirox olamine cream twice weekly for 24 weeks | 40% (23/57*); 8-point assessment scale | 57 | Pruritus (18), burning sensation (17), folliculitis (1), herpes (1) |
| Vulvar lichen sclerosus | Li *et al.* (2013) | Open-label trial | 0.03% tacrolimus ointment twice weekly for 24 weeks | 22% (2/9) | 9 | Hyperpigmentation (1) |
| | Virgili *et al.* (2013) | RCT | 0.1% mometasone furoate ointment twice weekly for 52 weeks | 0% (0/7); GOS | 8 | None observed |
| | Corazza *et al.* (2015) | Open-label trial | 0.1% mometasone furoate ointment twice weekly for 52 weeks | 5% (1/22); GOS | 24 | None observed |
| | | | 0.05% clobetasol propionate ointment twice weekly for 52 weeks | 9% (2/22); GOS | 24 | None observed |
| Condylomata acuminata | Carpiniello *et al.* (1988) | RCT | ($CO_2$ laser followed by) 5% 5-fluorouracil every other day for 1 month | 71% (N/A), visual assessment | 27 | N/A |
| | Schöfer *et al.* (2006) | Trial with open-label and randomized arms | (Ablative treatment followed by) 5% imiquimod cream (frequency unknown) | 9% (6/71); N/A | 72 | N/A |
| | On *et al.* (2014) | Single-blinded RCT | (Two cycles of cryotherapy followed by) 15% sinecatechins ointment twice daily for up to 16 weeks | No data; visual assessment | 21 | Erythema (N/A), oedema (N/A), scaling (N/A), crusting (N/A), erosions (N/A) |
| | Puviani *et al.* (2018) | Masked-assessment RCT | ($CO_2$ laser followed by) 10% sinecatechins ointment twice daily for 12 weeks | 5% (3/59), visual assessment | 60 | Erythema or burning sensation (34) |

*DB – double-blind, PC – placebo-controlled, RCT – randomized clinical trial, PGA – Physician's Global Assessment scale, IGA – Investigator's Global Assessment scale, N/A – data not available, GOS – Global Objective Scale. *The number of patients enrolled into the maintenance phase instead of these completing the trial.*

analysed for management of dermatological diseases retrieved from search and summarized in Table 2.

## Proactive therapy in dermatologic conditions

### Atopic dermatitis

AD is a chronic inflammatory skin condition which manifests by pruritic eczematous lesions recurring in typical locations. Various processes lead to persistent subclinical inflammation of unaltered and clinically normal-appearing skin of patients with AD [14]. Reactive treatment of AD usually involves corticosteroids and/or calcineurin inhibitors [15]. Symptomatic AD and higher AD severity was shown to have a negative impact on various aspects of patients' quality of life [16, 17].

In 2011, Schmitt *et al.* [14] conducted a meta-analysis of eight randomized controlled trials (RCTs) that included four studies of topical 0.005% fluticasone propionate ointment [3, 5, 18] and/or 0.05% fluticasone propionate cream [4, 5], three trials of tacrolimus ointment (children: 0.03%; adults: 0.1% concentration) [2, 19–21] and one of 0.1% methylprednisolone aceponate cream. The duration of treatment with topical corticosteroids was 16–20 weeks (applied twice weekly) and 40–52 weeks in the tacrolimus scheme (applied two or three times a week). The results indicated that each proactive approach was significantly superior in preventing flares compared with placebo and that fluticasone propionate (pooled relative risk = 0.46; 95% confidence interval (CI): 0.38–0.55) may be more efficacious in maintaining remission than tacrolimus (pooled relative risk = 0.78; 95% CI: 0.60–1.00). The most frequent AEs during topical corticosteroid therapy included respiratory tract infections and ear, nose, and throat symptoms, while in the tacrolimus scheme the most common were burning sensations, pruritus, and skin infections [22].

In 2022, a Cochrane systematic review of topical corticosteroid use in children and adults with mild to severe AD was published [23]. Pooled analysis of 7 RCTs revealed that proactive ('weekend') therapy lasting 16–20 weeks decreased the likelihood of relapse from 58% to 25% (moderate-level evidence; relative risk, 0.43; 95% CI: 0.32–0.57). No cases of cutaneous atrophy or new cases of abnormal cortisol levels were reported (low-level evidence). There were no data on clinically relevant adrenal suppression or influence on growth. In the recent 4-week open-label RCT on a paediatric group, proactive therapy showed a lower relapse rate and prevented worsening of itching in comparison to rank-down treatment (betamethasone valerate followed by hydrocortisone butyrate once daily) [24].

Although no head-to-head clinical trials of topical corticosteroids and tacrolimus were published to date, some studies comparatively analysed their impact on the epidermal barrier. In quiescent patients (i.e. with no active AD lesions), topical corticosteroids were associated with loss of skin barrier integrity, while tacrolimus was shown to preserve barrier function and improve the hydration of stratum corneum [25, 26]. In optical coherence tomography, a two-week course of corticosteroids caused transient subclinical epidermal thinning [27] while a 12-week proactive application of betamethasone valerate showed substantial thinning, which was insignificant regarding hydrocortisone acetate and methylprednisolone aceponate [28]. Epidermal thinning returned to baseline within 4 weeks and was not observed during the tacrolimus use [27, 28].

Recently, a comparative trial by Suehiro *et al.* [29] regarding AD maintenance with delgocitinib (a JAK inhibitor) versus tacrolimus ointment twice weekly for 4 weeks has been published. Superiority of tacrolimus in subjective and visible improvement was noted, however, the results did not reach statistical significance.

The proactive approach has been widely investigated for AD and it is recommended in European guidelines for maintenance of moderate-to-severe AD [15]. It is recommended to find the personal maintenance regimen, usually varying between once weekly to three times a week applications [2].

### Psoriasis vulgaris

Psoriasis vulgaris is a chronic, autoimmune skin disease characterized by the presence of erythematous plaques arising primarily on the scalp and extensor surfaces of the glabrous skin [30]. Current topical treatment guidelines include a combination of corticosteroids with vitamin $D_3$ analogues and calcineurin inhibitors for sensitive areas such as the face and the anogenital region [9, 31]. Management of psoriasis frequently causes therapeutic concerns and puts a serious burden on the patients [32] including adolescents facing the difficult transition period between childhood and adulthood [33]. Long-term maintenance therapies have been studied in psoriasis since the 1970s but used daily application of active substances, often on still affected skin [34]. The first literature report of 'weekend' maintenance therapy was published by Katz *et al.* [35] in 1991 as a double-blind placebo-controlled RCT. This study assessed the efficacy of weekend application (3 doses every 12 h, once a week) of 0.05% betamethasone dipropionate ointment on clear or almost-clear skin during the 24-week period, following a 3 or 4-week reactive treatment. Katz *et al.* [35] showed that the maintenance was effective ($p < 0.001$) with a relapse rate of 35% and no AEs observed.

The first reported study in psoriasis clearly labelled as proactive therapy was published in 2020 by Lebwohl *et al.* [36] as a protocol-registered [37] double-blind placebo-controlled RCT. This study assessed the twice-weekly application of a combination of 0.005% calcipotriene and 0.064% betamethasone dipropionate foam on clear or almost-clear skin (assessed in Physician's Global Assessment score; PGA < 2) during a 52-week period, following

a 4-week reactive treatment. The risk of treatment-related AEs was similar in both groups. Effects on the hypothalamus-pituitary-adrenal axis, calcium metabolism and new AEs were not clinically significant [38]. Patients in the proactive group had 43% lower risk of relapse (hazard ratio, 0.57; 95% CI: 0.47–0.69; $p < 0.001$) and achieved 26 extra days without recurrence in comparison to the control group, corresponding to a 41-day longer remission phase over 1 year (assessed in PGA score). Improvement in health-related quality of life scores was noted [32]. The limitation of this trial is a substantial drop-out rate (54%) resulting from not achieving the clear or almost clear PGA score by the patients.

Proactive therapy may be successful in controlling disease in a considerable subset of patients with psoriasis, especially for lesions in challenging areas such as hands, elbows and, feet [39]. Psoriasis rebounds, i.e. flares associated with abrupt withdrawal of reactive treatment that are more severe than the baseline manifestation [6] (defined as mPASI score ≥ 12 or ≥ 125% of the baseline in the study by Lebwohl *et al.* [36]) were less common in the proactive group than in the placebo group. Typical steroid-related skin side effects were not observed [40], which could supposedly result from a minimal-dose and intermittent corticosteroid application or the possible modulatory effect of calcipotriene [41]. In matching-adjusted indirect comparison analysis, the calcipotriene-betamethasone dipropionate foam approach showed a greater efficacy and more favourable safety profile than halobetasol propionate-tazarotene lotion therapy [42]. Calcipotriene-betamethasone dipropionate foam seems to be a good candidate for the proactive therapy in psoriasis as it was previously observed to be more effective than the gel-based alternative [43–45]. The foam formulation is also superior to gel regarding relieving pruritus [44, 45] and achieving immediate relief [45, 46]. Moreover, the foam fits in line with proactive foundations and patients' preferences to use the topicals which are fast to apply, non-greasy, and quickly absorbing [43]. A two-compound topical is also a cost-effective treatment in comparison to the simultaneous use of two separate medications [34].

### Seborrheic dermatitis

Seborrheic dermatitis is a chronic relapsing skin disease affecting sebaceous areas and manifesting with erythema, flaky scales, and pruritus. The standard first-line treatment involves emollients and antifungals as well as anti-inflammatory agents (e.g. corticosteroids and calcineurin inhibitors) [47].

Proactive therapy in seborrheic dermatitis was firstly studied in a double-blinded, placebo-controlled RCT published in 2013 by Kim *et al.* [48]. Patients were randomized to one of three treatment groups: 0.1% tacrolimus ointment applied twice-weekly, 0.1% tacrolimus ointment applied once-weekly, and placebo ointment applied twice-weekly for 10 weeks. Significant improvement of clinical symptoms (assessed in a four-point scale of erythema, pruritus, and scaling) was noticed in both tacrolimus groups, but not in the placebo group. The recurrence rate was the highest in the placebo group (80%), then in the once-a-week tacrolimus group (52%), and the lowest in the twice-weekly tacrolimus group (32%; $p < 0.05$ between each group; assessed in Investigator's Global Assessment scale, IGA). The AEs of proactive maintenance appeared in 21% of patients (mainly burning or tingling sensations), but they were transient, local, and in most cases did not prompt cessation of treatment. However, the statistical methods used in this study seem to be inadequate and the recurrence rates raise concerns.

In 2021, Joly *et al.* [49] performed a double-blind RCT using 0.1% tacrolimus ointment or 1% ciclopirox olamine cream applied twice-weekly for a 24-week maintenance, following a 1-week reactive therapy with 0.05% desonide. Patients were randomized to these two groups after achieving a complete or almost complete clearance (≤ 1 score in an 8-point assessment scale). Tacrolimus was found to be more effective than ciclopirox olamine (21% vs. 40% relapse rates; relapse defined as ≥ 3 score in an 8-point assessment scale), corresponding to a mean 64.5-day longer remission phase and a lower risk of relapse (hazard ratio = 0.47; 95% CI: 0.26–0.83; $p = 0.010$; adjusted for patients completing the study). Over a half of the patients in both groups experienced similar AEs such as pruritus and a burning sensation. Lack of a placebo control group is a limitation of this trial.

Proactive therapy based on tacrolimus showed promising outcomes to be regularly implemented in the clinical setting, indicating the superiority over the standard approach for facial seborrheic dermatitis. Large-scale and long-term follow-up clinical trials are necessary to establish the exact efficacy of the therapy [48].

### Anogenital lichen sclerosus

Anogenital lichen sclerosus is a chronic, inflammatory skin disorder characterized by the presence of itchy, atrophic patches or plaques. The mainstay of treatment is a topical application of potent or ultra-potent corticosteroids [50]. Proactive maintenance is crucial for anogenital lichen sclerosus as besides its recurring and distressing nature, untreated or irregularly treated lesions may progress to squamous cell carcinoma as a result of chronic inflammation or HPV infection [51–54].

In the first randomized trial published by Virgili *et al.* [55] in 2013, patients who had responded to 12-week reactive treatment were enrolled in a 52-week maintenance therapy of vulvar lichen sclerosus (< 3 in every category or a total ≤ 4 points assessed in the Global Objective Scale, GOS). Patients were randomized to one of three treatment groups: with topical mometasone furoate 0.1% ointment administered twice weekly, cold cream applied once daily, and topical vitamin E oil used once daily. The

relapse rates were higher in the cold cream group (62%, $p = 0.043$) and in the vitamin E group (56%, however results were not statistically significant, $p = 0.065$) compared to the proactive group with a topical corticosteroid, in which no case of relapse was observed (defined as GOS ≥ 5 or 3 points for any four signs; odds ratio = 0.0951; 95% CI: 0.0177–0.5106). No AEs were reported in any of the groups. A limitation of this study is a small sample size.

In 2015, Corazza *et al.* [56] performed an open-label comparative trial to assess the effectiveness and safety profiles of two topical corticosteroids in the proactive therapy of vulvar lichen sclerosus – 0.1% mometasone furoate ointment and 0.05% clobetasol propionate ointment. Patients who achieved remission in the 12-week reactive phase of treatment were enrolled in a 52-week maintenance therapy with continuation of the previously used topical corticosteroid twice weekly. The authors found that the disease had recurred in overall 6% of all patients, with 8% of patients in the clobetasol propionate group and 4% in the mometasone furoate group ($p > 0.999$, defined as ≥ 5 or 3 points for any four signs assessed in GOS). Mean time to relapse was 30 weeks with no significant differences between these two groups ($p = 0.794$). No AEs were observed. This study is limited by lack of patient randomization.

In an open-label trial from 2013, Li *et al.* [57] studied the proactive use of 0.03% tacrolimus ointment twice a week for a 6-month treatment of anogenital lichen sclerosus in prepubertal girls, after a 16-week reactive therapy. The severity of adverse skin reactions were assessed visually by a physician in a 4-point scale. Subjective symptoms were graded by the patients also in a 4-point scale. Relapses occurred in 22% of patients in the proactive group vs 80% of patients in the group lacking maintenance ($p = 0.036$). There was no significant difference in the efficacy of treatment between the two groups ($p = 0.134$). Only 1 case of AE (hyperpigmentation) was observed. The authors suggested that 0.03% tacrolimus ointment could be preferable to 0.1% tacrolimus ointment for the proactive therapy to reduce the possibility of AEs associated with percutaneous absorption of the drug in peri-mucosal areas. A limitation of this study is a small sample size.

The results of the trials indicate that potent corticosteroids are considered more effective than tacrolimus in proactive treatment of anogenital lichen sclerosus [58]. An individualized proactive treatment scheme is recommended in the current European guidelines [52, 58].

### Condylomata acuminata

Condylomata acuminata are epidermal papules caused by HPV and one of the most common sexually transmitted infections [59]. Treatment modalities leading to complete removal of the lesions include ablative techniques (e.g. cryotherapy, carbon dioxide or erbium lasers, electrocautery, photodynamic therapy) or surgical excision [60]. Due to the limitations of the single-method approach, a concept of sequential treatment was proposed. It implements immunomodulatory therapy (imiquimod, sinecatechins, podophyllotoxin, 5-fluorouracil) administered soon after the wound from ablative treatment is healed [61–63]. Available reports on maintenance therapy involve immunomodulatory drug application at least once daily, and therefore fail to strictly fit into the principles of the proactive approach. However, the available data on sequential therapy were summarized in this scoping review as they could prove a successful way of preventing recurrence of condylomata acuminata.

The most recent network meta-analysis of double-blinded RCTs was conducted in 2020 by Bertolotti *et al.* [63] and showed the efficacy of sequential therapies (ablation with imiquimod [64], $CO_2$ laser with 5-fluorouracil [65], $CO_2$ laser with sinecatechins [66]). Compared to placebo, surgery alone (pooled relative risk = 10.54; 95% CI: 4.53–24.52) was superior to ablative therapy with imiquimod (pooled relative risk = 7.52; 95% CI: 4.53–24.52), which was the most efficacious among sequential therapies. However, Schöfer *et al.* [64] defined ablative treatment as electrocautery, cryotherapy, laser therapy, or surgery, and only 63% of patients in the group of combined treatment with imiquimod received electrocautery [67]. In another study, Carpiniello *et al.* [65] suggested that penile condylomas were possibly recalcitrant to the therapy with $CO_2$ laser and 5-fluorouracil due to urethral reservoir of the HPV [65]. On *et al.* [66] noted that for cryotherapy with sinecatechins application, a complete clearance was reached by participants with fewer lesions at baseline as compared to the average number of lesions in each group. Additionally, On *et al.* [66] suggested that more severe cases benefited more from the combined approach. The AEs of topical imiquimod are hypopigmentation, local inflammation, and systemic fever-like symptoms, while sinecatechins are not associated with these side effects [64, 68]. The conclusions of this meta-analysis are limited by a high risk of bias of the included RCTs.

One trial was excluded from the meta-analysis due to lack of double blinding. In this study by Puviani *et al.* [61] from 2018, 10% topical sinecatechins were administered twice a day for 3 months, 2 weeks after $CO_2$ laser treatment. The recurrence rate in the treatment group was 5% vs. 29% in the control group (odds ratio = 0.16; 95% CI: 0.04–0.68; $p = 0.0024$). In the topical sinecatechins group, 55% of patients reported mild to moderate AEs like erythema and burning sensations. The limitation of this study is a masked-assessment maintenance phase, and a relatively small sample size.

Despite high efficacy of continuous sequential therapy, most trials identified a considerable rate of AEs. Consequently, these substances are not guideline-recommended as the first-line treatment of condylomata

acuminata owing to a lower benefit-risk ratio [62, 69]. Evidence regarding 5-fluorouracil is weak, while podophyllin is not suitable for patient self-application as it may contain potentially carcinogenic ingredients and cause systemic toxicity. The meta-analysis [63] highlights the need for further investigations in order to comparatively confirm the effectiveness and side effects of the sequential therapies [67].

## Conclusions

Proactive therapy is a developing concept that is likely to be adopted for various relapsing inflammatory and infectious dermatoses in the future. Available evidence indicates that the proactive therapy may significantly extend the time to relapse, whilst showing a favourable safety profile and predominantly local adverse effects. Cutaneous atrophy or hypothalamus pituitary-adrenal axis suppression were not observed during proactive corticosteroid use. Proactive therapy may improve patients' quality of life by achieving long disease-free periods and limiting the need for reactive treatment.

## Conflict of interest

KM and JN declare no conflict of interest. LB: invited speaker – AbbVie, Sanofi. LR: member of advisory boards – Janssen Pharmaceutical Companies, L'Oréal, Leo, Lilly, Pfizer, Sanofi, Novartis, UCB, Timber Pharma; invited speaker – Leo, AbbVie, L'Oréal, Lilly, Pierre Fabre.

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