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DOES PROACTIVE THERAPY REDUCE RELAPSE IN ATOPIC DERMATITIS? A SYSTEMATIC REVIEW AND META-ANALYSIS

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Abstract:*Background: Atopic dermatitis (AD) is a chronic inflammatory skin disease characterized by a high rate of relapse. Proactive therapy, involving intermittent application of topical anti-inflammatory agents after clinical remission, was developed to suppress subclinical inflammation and prevent relapse. Objective: This study aimed to evaluate the efficacy and safety of proactive maintenance therapy compared to reactive therapy in preventing relapse in AD patients. Methods: A systematic review and meta-analysis was conducted following PRISMA 2020 guidelines. Databases searched included PubMed, CENTRAL, ClinicalTrials.gov, and OpenAlex. Inclusion criteria were RCTs comparing proactive therapy versus reactive/emollient control in stabilized patients. Outcomes were analyzed using random-effects models. Results: Eight RCTs were included. Meta-analysis showed proactive therapy was associated with a significant reduction in relapse rate (Odds Ratio = 0.31; 95% CI 0.17–0.58; p<0.001) and prolongation of time to first relapse (Hazard Ratio = 0.16; 95% CI 0.04–0.60; p=0.007). Individual studies consistently demonstrated prolonged remission with both TCS and TCI. The safety profile was favorable with no evidence of skin atrophy in long-term use. Conclusion: Proactive therapy is an effective evidence-based strategy for long-term AD control, reducing significantly relapse frequency without clear evidence of increased serious adverse events during the reported study durations*

Keywords: *Atopic Dermatitis; Proactive Therapy; Maintenance Therapy; Relapse; Randomized Controlled Trials*

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INTRODUCTION

Atopic dermatitis (AD) is a complex chronic inflammatory skin disease and one of the most common dermatological conditions worldwide. Its pathophysiology is multifactorial and involves a dynamic interaction between epidermal barrier dysfunction, immune dysregulation, and environmental factors (Langan et al., 2020; Guttman-Yassky et al., 2017). Clinically, AD is characterized by intense pruritus, xerosis, and eczematous lesions that can significantly impact quality of life (Langan et al., 2020). The prevalence of AD is estimated to be 15–20% in children and 2–10% in adults in high-income countries (Langan et al., 2020; Silverberg, 2017). These findings demonstrate that AD is not only a clinical problem

associated with skin manifestations but also a chronic condition requiring long-term management to maintain disease control.

Historically, AD management has generally employed a reactive therapy approach, where treatment is administered when clinical symptoms or exacerbations appear (Wollenberg et al., 2018). While this approach is effective in controlling acute inflammation, it can be followed by repeated cycles of remission and relapse, known as a "roller-coaster" effect (Wollenberg & Bieber, 2009). Advances in understanding the immunopathogenesis of AD have shown that clinically normal-appearing skin in AD patients can still undergo pathological changes. This non-lesional skin can exhibit extensive terminal differentiation defects and a variety of immune abnormalities, including the persistence of subclinical inflammation (Suárez-Fariñas et al., 2011; Guttman-Yassky et al., 2019). This phenomenon suggests that the clinical disappearance of lesions does not necessarily indicate complete resolution of the disease process.

These issues underlie the need for a management approach that focuses beyond treatment when a relapse occurs. Reactive therapy has limitations because treatment is only administered after clinical manifestations appear, and therefore is not specifically directed at suppressing subclinical inflammation in previously lesioned skin areas (Wollenberg et al., 2018; Wollenberg & Bieber, 2009). This condition can maintain the recurring pattern of relapses and remissions in AD. Therefore, strategies are needed that can maintain remission after acute inflammation has been successfully controlled.

To address these limitations, a proactive therapy strategy was developed as a two-phase approach: remission induction followed by intermittent maintenance therapy, typically twice weekly, on previously affected skin areas (Wollenberg & Bieber, 2009; Wollenberg et al., 2008). This approach aims to suppress subclinical inflammation and prevent the recurrence of disease manifestations. However, the effectiveness and safety of this strategy need to be assessed based on evidence from randomized controlled trials, particularly when comparing it with reactive therapy or the use of emollients alone in pediatric and adult patients with stable AD. Such assessment is crucial to determine the extent to which proactive topical therapy can reduce the risk of relapse and prolong the time to the first relapse.

This study aimed to evaluate the effectiveness and safety of proactive topical therapy in preventing AD relapses compared with reactive therapy or emollient-based therapy alone, and to measure the reduction in relapse rates and time to first relapse based on evidence from randomized controlled trials. This study is urgent because AD control requires not only managing inflammation when symptoms appear but also maintenance strategies to maintain remission and break the cycle of relapse. The novelty of this study lies in the systematic synthesis of evidence from randomized controlled trials that specifically assess the effectiveness and safety of proactive topical therapy in children and adults with stable AD, thus providing a more targeted evidence base for determining long-term AD management strategies.

RESEARCH METHODS

This study is a systematic review following the PRISMA 2020 guidelines (Page et al., 2021) and has been registered in PROSPERO with number CRD420261287389. The study only included randomized controlled trials (RCTs) evaluating proactive topical therapy in

patients with atopic dermatitis (AD), while observational studies, case reports, non-randomized trials, and narrative reviews were excluded.

The study population included infants, children, adolescents, and adults diagnosed with AD based on standard clinical criteria. The sample consisted of RCTs in patients with moderate to severe AD who had experienced stabilization or remission of acute lesions. Interventions included proactive therapy using topical corticosteroids (TCS) or topical calcineurin inhibitors (TCI), while comparators included reactive therapy or emollients alone (Wollenberg & Bieber, 2009; Wollenberg et al., 2008).

Data were collected using a standardized extraction form that included study characteristics, population, intervention, comparator, relapse outcomes, time to relapse, and safety. Risk of bias was assessed using the Cochrane Risk of Bias 2 (RoB 2). Analysis used the Odds Ratio (OR) for relapse rate and Hazard Ratio (HR) for time to first relapse. Synthesis was performed narratively, and meta-analysis used a random-effects model, with heterogeneity assessed using the I^2 statistic (Schmitt et al., 2011; Lax et al., 2022).

A literature search was conducted using PubMed/MEDLINE, CENTRAL, ClinicalTrials.gov, and OpenAlex, as well as through searches of reference lists of relevant studies. Two reviewers independently screened titles, abstracts, and full texts based on predetermined criteria. Discrepancies were resolved through consensus or a third reviewer, and the selection process was documented using a PRISMA flowchart (Page et al., 2021).

RESULTS AND DISCUSSION

Study Selection

The systematic search of electronic databases and reference lists yielded a comprehensive set of records. After removing duplicates and screening titles/abstracts, eight randomized controlled trials were identified as meeting the predefined inclusion criteria for this review. These eight studies specifically compared a proactive maintenance regimen against a reactive/vehicle control in patients with stabilized atopic dermatitis. The study selection process is summarized in the PRISMA flow diagram (Figure 1).

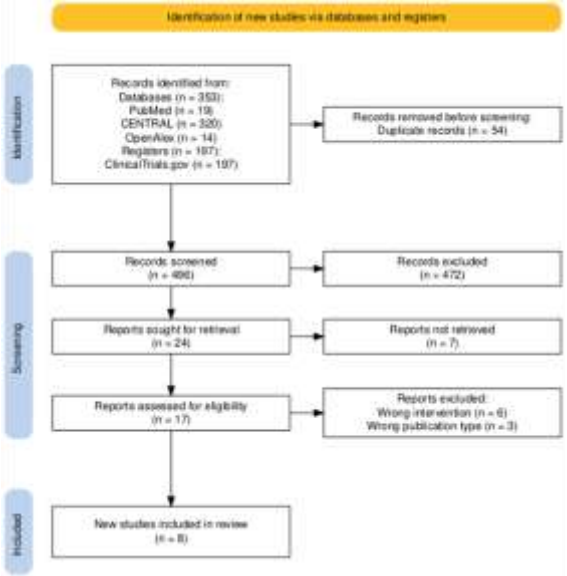


Figure 1: PRISMA flow diagram of study selection

Study Characteristics

The eight included studies represent the pivotal evidence base for proactive therapy. They can be categorized by the pharmacological agent used: Topical Calcineurin Inhibitors (Tacrolimus) and Topical Corticosteroids (Fluticasone Propionate, Methylprednisolone Aceponate). Table 1 provides a detailed summary of the characteristics of these included studies.

Table 1: Characteristics of Included Studies

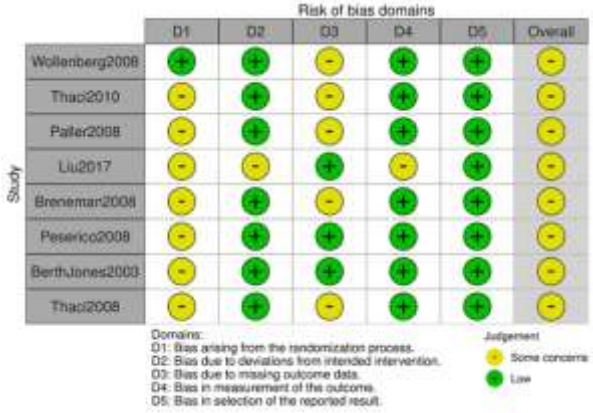
Study ID	Design	Population	Sample Size (N)	Intervention (Proactive)	Comparator (Reactive/Vehicle)	Maintenance Duration	Primary Outcome
Wollenberg 2008	RCT, DB, PC	Adults (16 years or older)	224	Tacrolimus 0.1% ointment (2x/week)	Vehicle ointment	12 months	Relapse rate; Time to first relapse
Thaci 2010	RCT, DB, PC	Children (2–15 years)	153	Tacrolimus 0.03% ointment (2x/week)	Vehicle ointment	12 months	Time to first relapse
Paller 2008	RCT, DB, PC	Children (2–15 years)	105	Tacrolimus 0.03% ointment (3x/week)	Vehicle ointment	40 weeks	Time to first relapse; Disease-free days
Liu 2017	RCT, OL*	Children (1–17 years)	107	Fluticasone propionate 0.05% cream (2x/week)	Emollient only	20 weeks	Relapse rate; Time to first relapse
Breneman 2008	RCT, DB, PC	Mixed (2 years or older)	197	Tacrolimus 0.03/0.1% ointment (3x/week)	Vehicle ointment	40 weeks	Time to first relapse
Peserico 2008	RCT, DB, PC	Mixed (12 years or older)	221	Methylprednisolone aceponate 0.1% (2x/week)	Emollient only	16 weeks	Time to first relapse
Berth-Jones 2003	RCT, DB, PC	Mixed (12–65 years)	295	Fluticasone propionate (2x/week)	Emollient only	16 weeks	Relapse rate; Time to first relapse
Thaci 2008	RCT, DB, PC	Children (2–15 years)	250	Tacrolimus 0.03% ointment (2x/week)	Vehicle ointment	12 months	Relapse rate; Time to first relapse

Abbreviations: RCT: Randomized Controlled Trial; DB: Double-Blind; PC: Placebo-Controlled; OL: Open-Label; AD: Atopic Dermatitis.

Risk of Bias in Studies

The risk of bias assessment using the Cochrane Risk of Bias 2 (RoB 2) tool indicated that all included studies were assessed as having some concerns overall. These judgments were primarily driven by concerns in the randomization process (Domain 1) and/or missing outcome data (Domain 3), which were common across trials. Other domains, including deviations from intended interventions, outcome measurement, and selective reporting, were generally assessed as low risk. The detailed domain-level assessment is presented in Table 2.

Table 2: Risk of Bias Assessment (RoB 2)



Results of Individual Studies

Eight randomized controlled trials were included in the systematic review. Due to heterogeneity in outcome definitions, reporting formats, and effect measures, not all studies were eligible for quantitative synthesis. Studies that did not contribute data suitable for meta-analysis are summarized descriptively in this section in accordance with PRISMA guidance.

Five clinical trials evaluated proactive maintenance therapy with tacrolimus in adult and pediatric populations based on relapse-related outcomes. Overall, proactive tacrolimus therapy consistently demonstrated better disease control than reactive or vehicle therapy (Wollenberg et al., 2008; Thaci et al., 2008; Thaci et al., 2010; Paller et al., 2008; Breneman et al., 2008).

In adult patients, proactive use of tacrolimus 0.1% has been shown to reduce disease exacerbations compared to vehicle (Wollenberg et al., 2008). In pediatric populations, proactive use of tacrolimus 0.03% has also been shown to reduce disease exacerbations compared to reactive therapy (Thaci et al., 2008; Thaci et al., 2010). Other studies have shown longer flare-free intervals, or days free of disease and flares, in patients receiving proactive therapy (Paller et al., 2008; Breneman et al., 2008). Although outcome measures differ across studies, all studies demonstrate the benefit of proactive therapy in maintaining disease control.

Three clinical trials evaluated proactive maintenance therapy using topical corticosteroids, namely fluticasone propionate and methylprednisolone aceponate, using outcomes related to recurrence. All studies demonstrated a benefit of proactive therapy compared with maintenance with emollients alone or reactive therapy (Berth-Jones et al., 2003; Peserico et al., 2008; Liu & Ong, 2018).

In adult and mixed populations, proactive use of fluticasone propionate was associated with a reduced incidence of relapses and a longer remission period compared to maintenance with emollients (Berth-Jones et al., 2003). Proactive therapy with methylprednisolone aceponate also showed fewer relapses and a higher chance of remaining relapse-free until the end of the maintenance period (Peserico et al., 2008). In pediatric populations, proactive fluticasone therapy showed a lower proportion of patients experiencing relapses during the maintenance phase compared to use of emollients alone (Liu & Ong, 2018). Differences in

definitions and reporting of outcomes meant that not all corticosteroid studies could be combined in a given analysis, but all studies showed results supporting proactive therapy.

Summary of Individual Study Findings

Across all included trials, proactive maintenance therapy—using either topical calcineurin inhibitors or topical corticosteroids—was associated with reduced relapse frequency, fewer disease exacerbations, longer flare-free intervals, or prolonged remission compared with reactive or emollient-only treatment. Despite heterogeneity in outcome measures and follow-up duration, the consistency of effect direction across studies supports the clinical benefit of proactive therapy in maintaining disease control.

Results of Synthesis

The synthesis of results is organized according to the two primary outcomes: relapse rate and time to first relapse. Individual study findings are presented descriptively, followed by quantitative synthesis where applicable.

1. **Relapse Rate (Odds Ratio Meta-analysis)**

   Relapse rate was analyzed as a dichotomous outcome and synthesized using odds ratios derived from the proportion of participants experiencing at least one relapse during the maintenance phase. Five randomized controlled trials contributed data to the meta-analysis. 8,10,13,14,16 Using a random-effects model, proactive therapy was associated with a statistically lower odds of relapse compared with reactive or emollient-only therapy (OR = 0.31; 95% CI 0.17–0.58; $p < 0.001$). This corresponds to an approximate 69% lower odds of relapse among patients receiving proactive maintenance treatment.

   Between-study heterogeneity was substantial ($I^2 = 79\%$), reflecting variability in population age (adults and pediatric patients), type of agent used (TCS and TCI), and duration of maintenance therapy. Despite substantial heterogeneity, the direction of effect consistently favored proactive therapy.

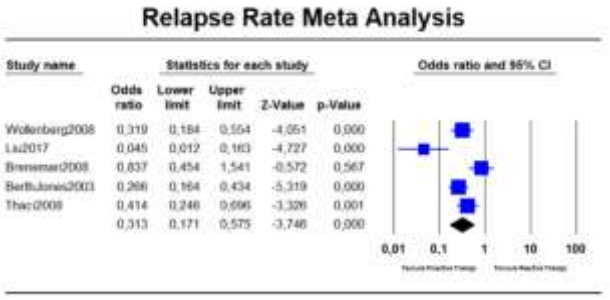


Figure 2. Forest plot of odds ratios for relapse during the maintenance phase comparing proactive therapy with reactive or emollient-only treatment (random-effects model).

2. **Time to First Relapse (Hazard Ratio Meta-analysis)**

   Time to first relapse was analyzed as a time-to-event outcome and synthesized using the hazard ratio (HR). Two randomized controlled trials provided data suitable for quantitative analysis (Peserico et al., 2008; Liu & Ong, 2018).

To maintain consistency across studies, hazard ratios were standardized so that values <1 consistently indicated a benefit of proactive therapy. In Liu and Ong (2018), the hazard ratio was initially reported with reactive therapy as the reference group (HR = 13.5; 95% CI 4.1–44.3), indicating a higher hazard of relapse in the reactive group compared to proactive therapy. This value was then mathematically inverted before being combined with the results of Peserico et al. (2008), who reported hazard ratios comparing proactive therapy to reactive therapy. The inversion results from Liu and Ong (2018) showed a higher hazard of relapse in proactive therapy compared to reactive therapy, with values <1 indicating a benefit of proactive therapy, while the standard error remained unchanged.

Based on a random-effects model, proactive therapy was associated with a significantly lower risk of recurrence compared to reactive therapy or emollients alone (HR = 0.16; 95% CI 0.04–0.60; p = 0.007). These results indicate that proactive therapy substantially prolonged the time to first recurrence compared to the comparison group (Peserico et al., 2008; Liu & Ong, 2018).

Between-study heterogeneity was substantial (I^2 = 75%), reflecting differences in study populations, intervention regimens, and follow-up duration. Despite this variability, both included studies demonstrated effects favoring proactive therapy.

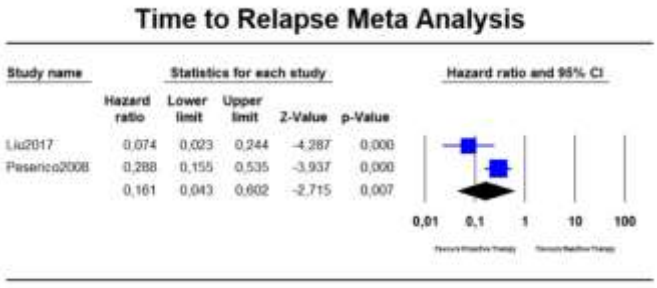


Figure 3. Forest plot of hazard ratios for time to first relapse comparing proactive therapy with reactive or emollient-only treatment (random-effects model).

Reporting Biases

Potential reporting bias was assessed for the relapse rate synthesis using visual inspection of a funnel plot of log odds ratios against their standard errors (Figure 4). The funnel plot did not demonstrate marked asymmetry; however, the small number of included studies (n = 5) substantially limits the reliability of visual assessment. Formal statistical tests for funnel plot asymmetry were not performed, as these are not recommended when fewer than 10 studies are available.

For the time-to-first-relapse synthesis, assessment of reporting bias was not feasible because only two studies contributed data, preceding meaningful visual or statistical evaluation of funnel plot asymmetry.

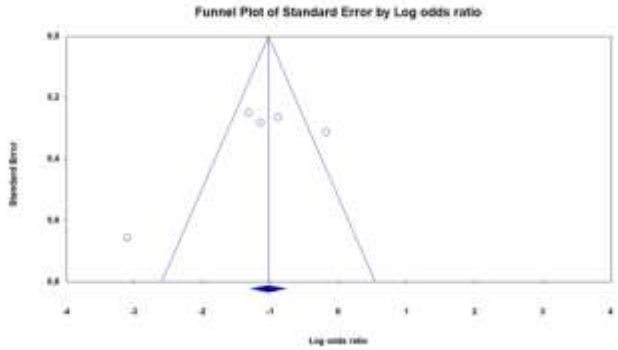


Figure 4: Funnel plot for relapse rate meta-analysis

Subgroup Analysis

The results showed consistent patterns across different age groups. Subgroup analyses based on age were conducted descriptively because the number of studies in each subgroup was insufficient for formal subgroup meta-analysis or statistical testing of interactions.

Children: Studies in pediatric populations, including those by Thaci et al. (2008, 2010), Paller et al. (2008), and Liu and Ong (2018), consistently demonstrate better disease control with proactive therapy using topical calcineurin inhibitors such as tacrolimus 0.03% or topical corticosteroids such as fluticasone. These studies demonstrated fewer relapses, reduced exacerbations, and longer flare-free intervals compared to reactive therapy or emollients alone (Thaci et al., 2008; Thaci et al., 2010; Paller et al., 2008; Liu & Ong, 2018).

Mature: Studies in adult and mixed-group populations, including Wollenberg et al. (2008), Breneman et al. (2008), and Berth-Jones et al. (2003), have shown a similar pattern of benefits from proactive therapy. In these studies, proactive therapy was associated with better delay in relapse and maintenance of remission compared to control therapy (Wollenberg et al., 2008; Breneman et al., 2008; Berth-Jones et al., 2003).

Overall, although the magnitude of the effects varied across studies, the direction of the effects showed a consistent pattern across both child and adult populations. These findings need to be interpreted descriptively and as a basis for generating further hypotheses.

Safety Outcomes

Safety outcomes were assessed descriptively across the included trials, as adverse event reporting was heterogeneous and not suitable for quantitative synthesis.

Topical Corticosteroids (TCS)

Safety assessments in studies evaluating proactive topical corticosteroid therapy have primarily focused on skin side effects associated with long-term corticosteroid use. In studies of fluticasone propionate and methylprednisolone aceponate, no cases of clinically significant skin atrophy, including telangiectasia, striae, or thinning, were observed in the proactive maintenance therapy group over the 16- to 20-week study period (Berth-Jones et al., 2003; Peserico et al., 2008; Liu & Ong, 2018).

Overall, the incidence of adverse events in the proactive therapy group was similar to or lower than in the emollient-only control group. Serious adverse events were rare or absent in the corticosteroid studies, and there was no consistent pattern of systemic side effects

associated with therapy. Intermittent administration, typically twice weekly, showed no evidence of cumulative corticosteroid toxicity during the maintenance phase (Berth-Jones et al., 2003; Peserico et al., 2008; Liu & Ong, 2018).

Topical Calcineurin Inhibitors (TCI)

In studies evaluating proactive tacrolimus therapy in adult and pediatric populations, the most frequently reported side effects were local reactions at the application site, such as burning, stinging, or pruritus. These reactions were generally mild to moderate in severity and transient (Wollenberg et al., 2008; Thaci et al., 2008; Thaci et al., 2010; Paller et al., 2008; Breneman et al., 2008).

The proportion of patients experiencing at least one adverse event was generally comparable between the proactive and reactive therapy groups. Serious adverse events were rare and inconsistently reported. In the studies that did report them, the number of serious adverse events was relatively small and did not show a consistent pattern suggesting systemic toxicity due to therapy. Treatment discontinuation due to adverse events was also low in both the proactive and control groups (Wollenberg et al., 2008; Thaci et al., 2008; Thaci et al., 2010; Paller et al., 2008; Breneman et al., 2008).

Summary of Security Findings

In both pharmacological groups, proactive maintenance therapy demonstrated a good tolerability profile over the 16-week to 12-month study period. Side effects were primarily mild and localized, while serious adverse events were rare and inconsistently reported. However, incomplete reporting of adverse events in some studies limits definitive comparisons between proactive and reactive therapy strategies (Wollenberg et al., 2008; Thaci et al., 2008; Thaci et al., 2010; Paller et al., 2008; Breneman et al., 2008).

Economic Analysis

Economic outcomes were reported in one study included in the systematic review. Thaci et al. (2010) evaluated the economic impact of proactive tacrolimus therapy in pediatric patients with atopic dermatitis. In that study, proactive therapy was associated with fewer disease flares and longer flare-free intervals without increasing overall treatment costs in patients with moderate disease. In patients with severe atopic dermatitis, proactive therapy was reported to be cost-effective over the study period (Thaci et al., 2010).

No other included studies formally reported economic outcomes or cost-effectiveness. Therefore, the economic findings in this systematic review are limited to a single study and should be interpreted accordingly.

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Discussion

Summary of Key Findings

This systematic review and meta-analysis synthesized evidence from eight randomized controlled trials evaluating proactive maintenance therapy for atopic dermatitis. Overall, proactive therapy using topical corticosteroids or topical calcineurin inhibitors consistently demonstrated better long-term disease control than reactive therapy or emollients alone. The quantitative synthesis demonstrated a reduction in relapses and a prolongation of the time to first relapse, while the narrative synthesis demonstrated a consistent trend of benefit across

outcomes, intervention types, and age groups.

Interpretation of Relapse Prevention and Time to Relapse

The reduction in relapse rates supports the concept that intermittent, scheduled anti-inflammatory therapy can suppress subclinical inflammation in previously lesioned skin. Reactive therapy, which discontinues anti-inflammatory therapy after clinical lesions have resolved, may allow subclinical inflammatory activity to persist unchecked, increasing the risk of relapse. Analysis of time to first relapse also demonstrated a lower risk of relapse and longer remission with proactive therapy. The heterogeneity observed is likely related to differences in study design, duration of maintenance, definition of relapse, and patient characteristics.

Mechanistic Considerations

The effectiveness of proactive therapy supports the concept of subclinical inflammation in atopic dermatitis. Skin that appears clinically unlesioned can still retain inflammatory infiltration and increased expression of proinflammatory cytokines, which can increase the risk of relapse (Suárez-Fariñas et al., 2011; Guttman-Yassky et al., 2019). Intermittent anti-inflammatory therapy in previously lesioned areas may help suppress residual immune activation and support the restoration of epidermal barrier function.

Comparison with Previous Literature

The results of this study align with previous systematic reviews and meta-analyses. Schmitt et al. (2011) showed that topical corticosteroids and topical calcineurin inhibitors were effective in reducing flares compared to reactive therapy. A Cochrane review by Lax et al. (2022) also showed a reduction in relapses with proactive weekend therapy compared to reactive therapy. These results are consistent with the findings of this study, which showed a reduction in relapses during the maintenance phase. This study also provides information on the time to first relapse, thus providing insight into the duration of remission, which can support patient counseling and shared decision-making.

Security Implications

Concerns about the safety of long-term topical anti-inflammatory therapy, particularly the fear of corticosteroid side effects, can be a barrier to implementing maintenance therapy. The results of this study suggest that proactive therapy administered intermittently has a good safety profile. In studies of proactive topical corticosteroid therapy, no cases of clinically significant skin atrophy were observed during the 16- to 20-week maintenance period. With topical calcineurin inhibitors, side effects were primarily mild and transient local reactions. Serious side effects were rare and did not demonstrate a consistent pattern of systemic toxicity.

Implications for Clinical Practice

Research findings support the implementation of a proactive maintenance strategy in the management of AD, particularly in patients with moderate to severe disease who frequently experience relapses after discontinuing therapy. The approach may involve controlling acute flares with daily application until lesions improve, followed by resuming

the same or an alternative agent at a lower frequency, typically twice weekly, to previously affected areas. Emollient use should continue daily. Both TCS and TCI have demonstrated efficacy in preventing relapses, with the choice of therapy tailored to lesion location, patient preference, and cost (Wollenberg et al., 2008; Thaci et al., 2008; Berth-Jones et al., 2003).

Limitations

This study has several limitations. First, the duration of the included studies ranged from 16 weeks to 12 months, and AD is a chronic condition requiring long-term management. Therefore, evidence beyond one year is limited. Second, most studies compared proactive therapy with vehicle or emollient alone, while studies directly comparing topical corticosteroids and topical calcineurin inhibitors are limited. Third, there were differences in the definition of relapse between studies, although the direction of effect consistently favored proactive therapy. Furthermore, assessment of reporting bias and economic outcomes was limited due to the relatively small number of available studies.

Although this systematic review was conducted and registered in 2026, the majority of eligible RCTs were published between 2003 and 2017. This reflects the early development of proactive maintenance therapies, which primarily evaluated topical corticosteroids and calcineurin inhibitors. Newer topical therapies, including Janus kinase inhibitors such as ruxolitinib and aryl hydrocarbon receptor agonists such as tapinarof, have been evaluated primarily through daily regimens for sustained disease control, rather than through intermittent proactive maintenance phases after disease stabilization. Therefore, these studies did not meet the criteria established in this systematic review.

The lack of numerous studies published between 2018 and 2026 likely reflects a shift in therapy development toward continuous maintenance strategies and a reduced use of reactive control groups in randomized trials. This does not indicate a selective selection of older studies. Although new therapeutic agents represent important developments in the long-term management of AD, randomized evidence specifically evaluating proactive or intermittent maintenance strategies remains limited. Future research is needed to evaluate whether the relapse prevention benefits found with corticosteroids and calcineurin inhibitors also apply to newer topical agents.

CONCLUSION

This systematic review and meta-analysis of eight randomized controlled trials confirms that proactive therapy is an effective and generally well-tolerated strategy for the long-term management of atopic dermatitis. By targeting the invisible but persistent subclinical inflammation in healed skin, proactive regimens with topical corticosteroids or topical calcineurin inhibitors significantly delay disease relapse and reduce the frequency of exacerbations compared to the reactive approaches. Importantly, this efficacy is achieved without a marked increase in adverse events such as skin atrophy or infection over the study period. Consequently, clinical guidelines and practice should consider the use of proactive therapy for patients with relapsing atopic dermatitis to break the cycle of flares and improve long-term quality of life.

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