

# Can Topical Corticosteroids Prevent the Relapse of Atopic Dermatitis?

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## Introduction:

Atopic dermatitis (AD) is a chronic, relapsing disease, often seen in pediatric patients, triggered by a combination of factors (genetics, the environment, skin barrier dysfunctions (even in normal uninvolved skin) and immunologic responses).<sup>1</sup>

There is currently no standard management plan for the long-term management of AD.<sup>2</sup>

The purpose of this study was to review the existing literature to determine how AD is managed long-term. A comprehensive systematic review published in 2000<sup>2</sup> found that most practitioners use one or two approaches for treating AD.

1. A potent topical corticosteroid (TCs) followed by a lower potency preparation as the condition improves
2. A short course of topical corticosteroid followed by a maintenance regimen of emollients.

Recently, topical immunomodulators (TIMs) or topical calcineurin inhibitors (TCIs) have become available for AD management.

## Long-Term Therapy Options

Currently there is no remedy or single treatment that can cure AD. Generally repeated treatments are necessary to achieve a stable state where flare-ups are controlled and the number reduced.

Individual treatments for a patient is dependent on factors such as disease severity, age, potential compliance problems, efficacy, safety data and treatment costs.

To prevent and reduce flares, long-term therapy regimens must be an ongoing daily occurrence with the use of emollients and then prescription medications being used to prevent and/or treat flare-ups.

## Search Criteria

The present literature was analyzed to understand the current therapy options for long-term management of AD.

The literature was examined following a search of MEDLINE and EMBASE databases. Search criteria included all articles on AD from January 1, 1995 to the present, published in English with human subjects including reviews, reports, and meta-analyses. One additional limit was then placed on the search to identify randomized, controlled trials only.

The search found 3525 papers published on atopic dermatitis of which 201 were randomized controlled trials. Sixty-two papers discussed AD and relapse, twenty-five discussed AD and long-term management and eighteen AD and intermittent therapy.

Two different long-term maintenance therapy options were apparent during the review of the literature, one using topical corticosteroids and the other a combination of topical immunomodulators and topical corticosteroids.

Interestingly, only two topical corticosteroids have been studied in intermittent long-term maintenance therapy.

Table 1: Clinical Papers on Long-term Therapy Options for AD

Long-term Maintenance Therapy Options	Total Number	Randomized Controlled	Non-Randomized Controlled
Fluticasone Propionate (intermittent)	4	4	0
Mometasone Furoate (intermittent)	2	0	2
Pimecrolimus +TCs rescue	5	5	0
Tacrolimus	1	0	1
Totals	12	9	3

## Long-Term Intermittent use of Topical Corticosteroids

Topical corticosteroids are the standard of care for AD. They are commonly used for short term (up to 4 weeks) control of an acute flare.<sup>2</sup>

Two topical corticosteroids have been shown to be efficacious and well tolerated for intermittent long-term therapy.<sup>2,3</sup>

Fluticasone propionate (FP) (eg. Cutivate) has been the most extensively studied TCs and has been shown to be effective as an intermittent/maintenance therapy to control moderate-severe AD (see Table 2).

Fluticasone propionate is one of the newer corticosteroids that has low systemic bioavailability and a low potential to produce side-effects.<sup>4,5</sup> Fluticasone propionate has been shown to be effective and safe in the treatment of moderate to severe AD when applied either once or twice daily, for up to four weeks. Studies have shown that topical fluticasone propionate has minimal potential for local effects including skin thinning.<sup>6,8</sup>

Mometasone furoate (MF) (eg. Elocom) has also been examined in open-label studies for maintenance therapy (See Table 3)

Collectively these studies show that topical corticosteroids can be used effectively in the long and short-term treatment of AD. These studies show that twice weekly application of potent topical corticosteroids may help to prevent relapse of AD.

## Long-Term Management with Topical Calcineurin Inhibitors

Both tacrolimus and pimecrolimus are members of this class. They are non-steroidal, anti-inflammatory drugs with numerous studies demonstrating their utility in the treatment of AD.<sup>14</sup>

Calcineurin inhibitors have been shown to reduce the extent, severity and symptoms of AD in adults and children. Pimecrolimus can be effective in reducing the severity of mild to moderate AD in children and adults.<sup>15,16</sup>

Pimecrolimus has been show to be useful, in conjunction with TCs as rescue therapy, in controlling chronic relapse of AD (Table 4). In these studies patients often needed TCs as rescue therapy for controlling flares. Suggests pimecrolimus has limited efficacy as monotherapy in long-term treatment of AD.

Tacrolimus had been examined in an open-label study.<sup>17</sup>

Table 2: Summary of three long-term clinical studies investigating twice weekly fluticasone propionate (FP) plus daily emollient maintenance therapy (long-term maintenance phase only)

Reference	Treatment (in addition to daily emollients) (AD was initially stabilized with daily FP bid 3-4 wks)	Duration of maintenance phase (after stabilization phase - up to weeks)	Age	No. Patients	Median Time to Relapse (weeks)	Relapse free at end of study
van der Meer <i>et al.</i> (1999) (ointment) <sup>6</sup>	FP once daily on 2 consecutive days per week vs base	16 weeks	15–46 yr	54	FP >16 Base 5.3	FP group 2.6 times more likely to be relapse free than base group
Hanifin <i>et al.</i> (2002) (cream) <sup>8</sup>	FP once daily on 2 days per week vs base	20 weeks	0.2–63 yr children adult	348 231 117	FP >20 Base 4.7	FP group 7.7 times more likely to be relapse free than base group
Berth-Jones <i>et al.</i> (2003) (cream & ointment) <sup>10</sup>	FP once daily on 2 consecutive days per week vs base	16 weeks	11–64 yr	295	FP >16 Base 6.1	FP cream group 5.8 and FP ointment 1.3 times more likely to be relapse free than base group

Safety/Tolerability: Studies showed no significant evidence of skin atrophy or other local or systemic (HPA axis) effects

Table 2b: Summary of one long-term study investigating on demand/as required\* use of fluticasone propionate, hydrocortisone butyrate (HCB) or hydrocortisone (HC) to daily emollient maintenance therapy to control flare and then to treat at first sign of symptoms

Reference	Treatment (in addition to daily emollients) (AD was initially stabilized with one study treatment bid for 2-4 wks)	Duration of maintenance phase (after stabilization phase - up to 4 weeks)	Age	No. Patients	Median Time to Relapse (weeks)	Outcome
Kirkup <i>et al.</i> (2003) (cream) <sup>11</sup>	FP vs HC up to twice daily as required/on-demand	12 weeks	2–14 yr	128	FP 8.9 HC 5.1	More patients on FP (66%) than on HC (38%) were judged much improved
Kirkup <i>et al.</i> (2003) (cream) <sup>11</sup>	FP vs HCB up to twice daily as required/on-demand	12 weeks	2–14 yr	137	FP 7.3 HCB 8.1	More patients on FP (98%) than on HCB (84%) were judged much improved/improved

Safety/Tolerability: Studies showed no significant evidence of skin atrophy.

\*for on-demand/as-required' use patients advised to use medication for up to twice daily at first sign of relapse.

Table 3: Summary of two long-term non-randomized studies investigating use of two-to-three times weekly mometasone furoate (MF) for maintenance therapy

Reference	Treatment (AD was initially stabilized with once daily MF for 3 wks)	Duration of maintenance phase (after stabilization phase – up to 30 weeks)	Age	No. Patients	Median Time to Relapse (Days)	Relapse free at end of study (% of patients)
Veien <i>et al.</i> (1999) (cream) <sup>12</sup>	MF once daily 2 or 3 times per week vs emollient	30 weeks	17–70 yr	120	not given	MF three times per week 83% MF twice per week 68% Emollient 26%
Faergemann <i>et al.</i> (2000) (cream) <sup>13</sup>	MF once daily 2 times per week vs base	24 weeks	17–63 yr	68	not given	MF 90%

Safety/Tolerability: Studies reported several instances of skin atrophy.

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Table 4: Summary of five long-term clinical studies investigating twice-daily pimecrolimus (P) at first sign or symptom of flare in conjunction with daily emollient therapy and moderately potent topical corticosteroids (TCs) as rescue of flare

Reference	Treatment (in addition to daily emollients)	Duration of Treatment	Age	No. Patients	Medication Treatment Days	Topical corticosteroid rescue use during study	Patients free of Relapse at end of study
Kapp <i>et al.</i> (2002) <sup>18</sup>	P twice daily until clear, if flare not controlled moderately potent TCs	1 year	.3–.23 yr	251		P group 36.3% of patients Control group 65.2% of patients	P 56.9% Control 28.3%
Wahn <i>et al.</i> (2002) <sup>19</sup>	P twice daily until clear, if flare not controlled moderately potent TCs	1 year	2–17 yr	439	P group 211.9 days Control group 156 days	P group 42.6% of patients Control group 68.4% of patients	P 50.8% Control 28.3%
Meurer <i>et al.</i> (2002) <sup>20</sup>	P twice daily until clear, if flare not controlled moderately potent TCs	24 weeks	adults	192		P group used TCs on 14.2% of days Control group used TCs on 37.2% of days	P 44.8% Control 18.8%
Meurer <i>et al.</i> (2004) <sup>21</sup>	P twice daily until clear, if flare not controlled moderately potent TCs	24 weeks	adults	130		P group used TCs on 9.7% of days Control group used TCs on 37.8% of days	P 59.7% Control 22.1%
Luger <i>et al.</i> (2004) <sup>22</sup>	P twice daily until clear of signs/symptoms	1 year	18–79	328	P used 88.7% of study days (324 days)	none	P 42%
Luger <i>et al.</i> (2004) <sup>22</sup>	Triamcinolone acetonide/hydrocortisone twice daily until clear of signs/symptoms	1 year	18–79	330	Triamcinolone acetonide/hydrocortisone used 83.4% of study days (304 days)	83.4% of study days	not given

Safety/Tolerability: S Study reported no clinically significant adverse events. N Study reported an increased incidence of skin viral infections over control. Y Study reported an increased incidence of papilloma and skin striae in TCs group. Triamcinolone acetonide is a moderately potent TCs.

## Discussion

Topical corticosteroids are widely prescribed for the treatment of AD and are considered to be the mainstay of AD therapy. They have been proven to be safe and efficacious in randomized, controlled trials for short-term (2 to 4 weeks) continuous use.<sup>2</sup>

The new TIMs, tacrolimus and pimecrolimus, have also been proven to be safe and efficacious in randomized, controlled trials for the short to medium term (6 months to 1 year) treatment of AD, and especially in the prevention of progression to flares.<sup>14</sup>

Randomized controlled clinical studies demonstrate that two long-term treatment options are viable for managing AD:

- (1) Fluticasone propionate twice weekly in addition to daily emollients decreases average time to relapse from 5-6 weeks to >16 weeks.
  - (a) Fluticasone propionate twice weekly was well tolerated by patients for up to 24 weeks with no reported incidence of skin atrophy or skin thinning.
  - (b) More studies are needed to evaluate the efficacy of other topical corticosteroids.
- (2) Pimecrolimus twice daily in addition to daily emollients and in conjunction with moderately potent topical corticosteroid as rescue medication.
  - (a) Pimecrolimus twice daily was well tolerated by patients for up to 1 year with a few studies reporting an increased incidence of skin viral infections.
  - (b) More studies are needed to evaluate the efficacy of tacrolimus.

Table 5: Comparison of medication usage between two long-term treatment options

Long-Term Management of AD	Treatments	Average Number of Treatments
Fluticasone propionate	All studies : Twice weekly for 16–20 weeks	32–40
Pimecrolimus + TCs rescue	Kapp <i>et al.</i> 2002: Twice daily for 188 days over 1 year Wahn <i>et al.</i> 2002: Twice daily for 211.9 days over 1 year Luger <i>et al.</i> 2004: Twice daily for 324 days over 1 year	376 423.8 648

## Conclusions

- The twice weekly fluticasone propionate maintenance regimen is able to preventing recurrent relapses of AD and therefore reduces the need for acute intensive short courses of daily topical corticosteroid
- Intermittent fluticasone propionate therapy is a viable option for long-term management of AD