Improvement in Treatment Adherence With a 3-Day Course of Fluocinonide Cream 0.1% for Atopic Dermatitis

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Variations in adherence may cause variations in treatment outcomes with topical corticosteroid therapy for atopic dermatitis. An intensive short course of outpatient treatment may promote good adherence and provide a high level of efficacy. The purpose of this study was to assess the efficacy, tolerability, and adherence to short-term treatment with fluocinonide cream 0.1% in the treatment of atopic dermatitis. Twenty participants with mild to severe atopic dermatitis were instructed to use fluocinonide cream 0.1% twice daily for 3 consecutive days for a total of 6 doses. Disease severity was assessed at baseline, day 3, day 7, and day 14. Electronic monitoring was used to measure adherence to treatment. Median adherence to treatment over the 3-day period was 100%. By day 14, the median visual analog scale (VAS) of pruritus and eczema area and severity index (EASI) scores improved from baseline by 79% and 76%, respectively. By the end of the study period, 11 participants had investigator global assessment (IGA) scores of clear or almost clear. The absolute degree of improvement was proportional to baseline disease severity. Short-term treatment with fluocinonide cream 0.1% for atopic dermatitis was well-tolerated and resulted in significant disease improvement (P<.001). Participants were highly adherent to the 3-day treatment regimen. Efforts to improve adherence may be valuable approaches for treating recalcitrant atopic dermatitis.

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Atopic dermatitis is a corticosteroid-responsive condition that rapidly clears when topical corticosteroids are applied during inpatient care.[1] Some patients seen in outpatient clinics do not improve as expected; in others, the effectiveness of topical corticosteroids wanes over time. The dogma of the past implicated a tolerance to topical cortisones via down-regulation of steroid receptors with chronic use of the medication. However, clinical trials have not identified such resistance.[2]

Patient adherence to topical medications for chronic skin conditions is especially poor.[3-6] Even when patients use their medications, there is variability in their dosing intervals and patients may take drug holidays lasting 3 days or more.[7] In patients with atopic dermatitis, it has been reported that adherence drops precipitously over the first 3 days of treatment.[4] Poor response to topical corticosteroids is likely due to poor adherence.[6]

Modifying patient adherence behavior may contribute to better clinical outcomes. Although adherence to topical therapy drops dramatically over the first few days, it increases shortly before return office visits, a phenomenon called white coat compliance.[8,9] Initial return visits for patients with atopic dermatitis

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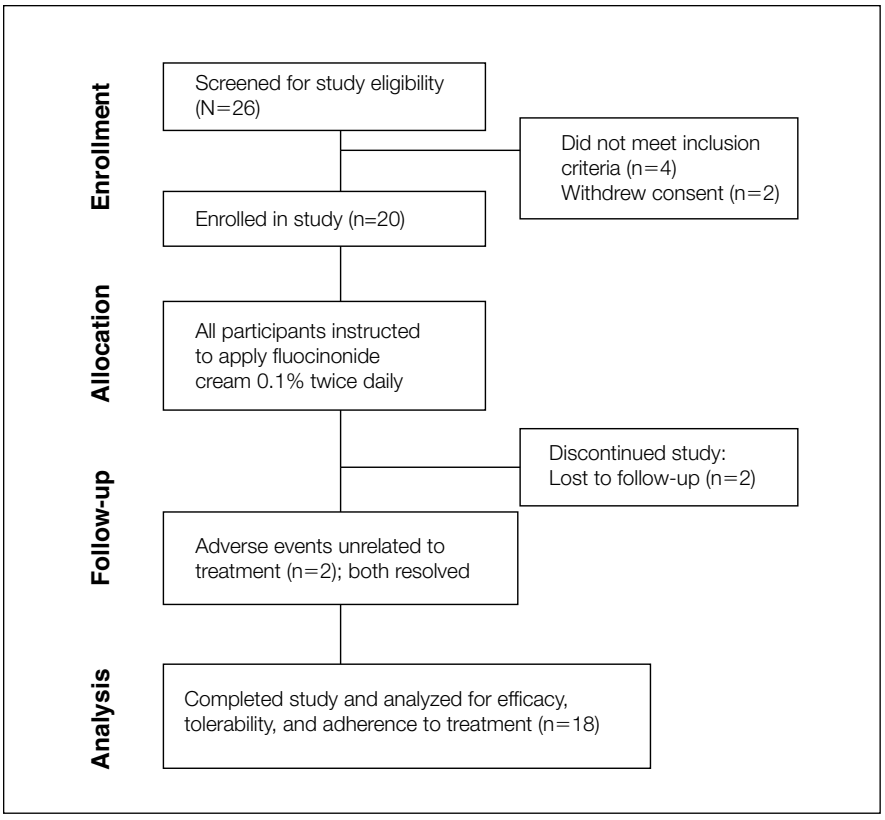

Figure 1. Consort flow diagram.

often occur weeks to months after the baseline visit. We hypothesize that patients will be more compliant with medication use over a short time ending in a return visit. We tested the prediction that patients would be far more adherent to treatment in a 3-day study than they would be over the first 3 days of an 8-week study. Such changes in the treatment course could be a low-cost, feasible means to enhance patient adherence and treatment outcomes.

Methods

Twenty-six individuals were screened for study eligibility, and 20 male and female participants 17 years and older with mild to severe atopic dermatitis were enrolled in this single-center, open-label study. Participants were included based on an investigator global assessment (IGA) of mild to severe disease (0=clear; 1=almost clear; 2=mild; 3=moderate; 4=severe) and involvement of at least 2% body surface area. Approval for this study was obtained from the Wake Forest University School of Medicine Institutional Review Board.

Individuals were excluded from participating in the study if they had used a systemic anti-inflammatory medication within the last 4 weeks, had used a topical corticosteroid or other anti-inflammatory medication within the last 2 weeks, had a disease severity requiring more than 60 g of cream in a 1-week period, had concurrent medical conditions that may have interfered with study outcomes or participant assessments, were pregnant or breastfeeding, or had a known allergy to the study medication or its components.

Participants were instructed to apply fluocinonide cream 0.1% twice daily on affected body surfaces for 3 consecutive days for a total of 6 applications. Follow-up visits were scheduled on study day 2 or day 3 depending on when the 6 doses were completed. Participants were allowed to use their own nonmedicated moisturizers over the course of the study.

Adherence to treatment was electronically monitored with Medication Event Monitoring System® caps that utilized a concealed microprocessor to record when the medication was opened. Participants were instructed to record their medication use in a diary and return the medication so that it could be weighed at the next visit. Electronic monitoring was not disclosed to the participants until the end of the study so that knowledge of these monitors would not bias adherence rates.

Disease severity was measured (N=18) using the visual analog scale (VAS) of pruritus (scale of 0–100 mm; higher number indicates worse pruritus), investigator global assessment of response to treatment (0=clear; 1=almost clear; 2=marked improvement; 3=moderate improvement; 4=slight improvement; 5=no change from baseline; 6=worse), IGA, and

Table 1.

Participant Demographics

Demographic	Enrolled Participants (N=20)
Sex, n (%)	
Male	11 (55)
Female	9 (45)
Age range, y	17–62
Median age, y	27
Race, n (%)	
White	9 (45)
Black	11 (55)
Lost to follow-up, n (%)	2 (10)

eczema area and severity index (EASI)(scale of 0–72; higher number indicates worse disease).[10] Participants were evaluated at baseline, day 2 or day 3 (depending on when the sixth dose was taken), day 7, and day 14 (or end of the study). On day 3 and day 14, participants assessed the severity of their atopic dermatitis using the subject global assessment of response to treatment (SGA) (0=clear; 1=almost clear; 2=marked improvement; 3=moderate improvement; 4=slight improvement; 5=no change from baseline; 6=worse).

All statistical analyses were performed using SAS 9.1 software. Wilcoxon signed rank tests were used to analyze improvements in assessments compared to baseline.

Results

Of the 20 participants enrolled, 18 completed the study (Table 1; Figure 1). The median adherence to treatment was 100% (mean, 93%) with a range of 50% (once daily) to 133% (more than twice daily on occasion). All participants used the medication at least once daily. Self-reported adherence was at

Table 2.

Assessments of Atopic Dermatitis Severity Over Time[a,b]

Assessment	Baseline	Day 3	Day 7	Day 14
IGA				
Median	2.5	2.0	1.5	1.0
Mean	2.6	1.8	1.6	1.4
95% CI	2.3-2.8	1.5-2.2	1.1-2.1	1.0-1.9
VAS				
Median	56	18	12	12
Mean	58	19	18	21
95% CI	49-67	11-28	7-29	8-35
EASI				
Median	4.1	1.6	1.3	1.0
Mean	5.1	2.4	1.7	1.7
95% CI	3.1-7.0	1.0-3.9	0.9-2.6	0.9-2.5

Abbreviations: IGA, investigator global assessment; CI, confidence interval; VAS, visual analog scale; EASI, eczema area and severity index.

[a]All measures showed significant improvement from baseline at each time point (Wilcoxon signed rank test, $P<.001$).

[b]IGA measured on a 5-point scale (0=clear; 1=almost clear; 2=mild; 3=moderate; 4=severe); VAS measured on a scale of 0–100 mm, with a higher number indicating worse pruritus; EASI measured on a scale of 0–72, with a higher number indicating worse disease.

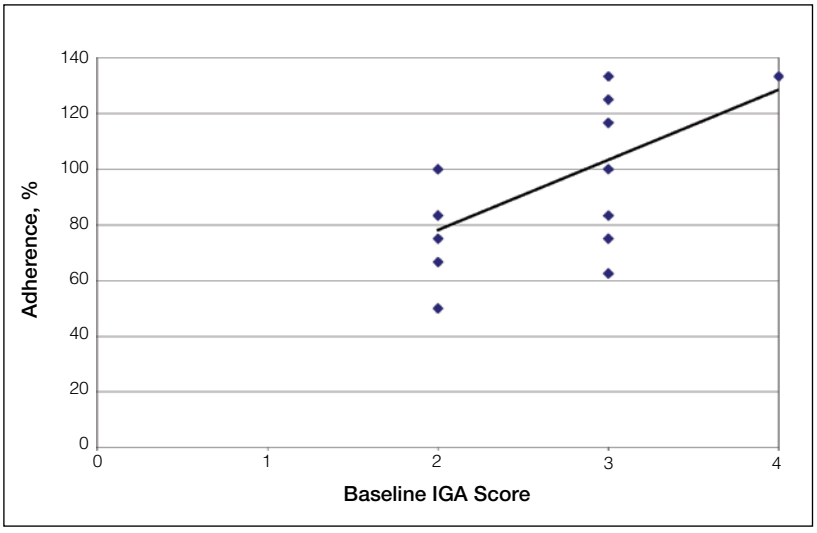

Figure 2. Adherence correlated with baseline disease severity measured using the investigator global assessment (IGA)(0=clear; 1=almost clear; 2=mild; 3=moderate; 4=severe). Participants with more severe disease had greater adherence to the 3-day treatment with fluocinonide cream 0.1% ($P<.01$). Solid line indicates linear trend.

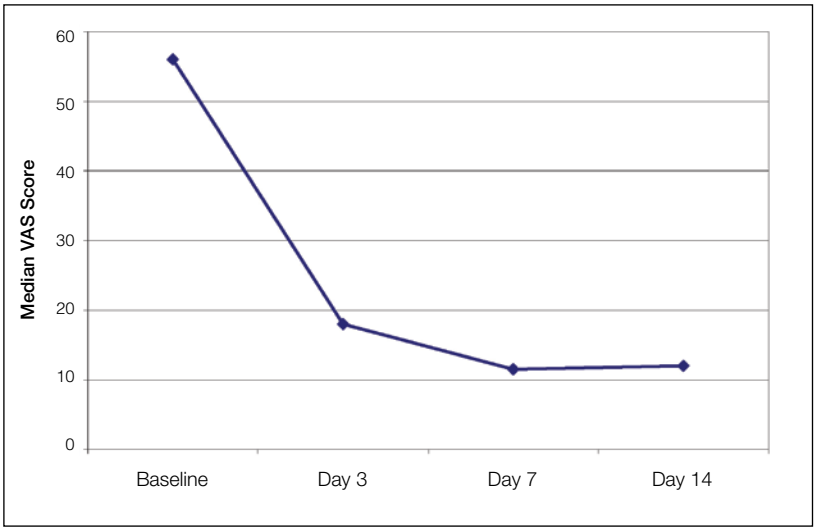

Figure 3. Improvement in median visual analog scale (VAS)(scale of 0–100 mm; higher number indicates worse pruritus) of pruritus scores over time. There was significant improvement from baseline for each time point ($P<.001$).

least 100% for all participants (6 of 6 doses), with 3 participants reporting use of a seventh dose. The baseline disease severity as rated by the IGA positively correlated with medication adherence; more severe baseline disease was associated with greater use of the medication ($P<.01$)(Figure 2).

In our small study, we did not find a notable impact of age or sex of the participant on clinical outcomes (IGA, VAS, EASI) or medication adherence. Scores for all measures improved from baseline to the end of the 14-day study (Table 2; Figures 3 and 4). By day 3, median IGA, VAS, and EASI scores improved by 20%, 68%, and 61%, respectively ($P<.001$). By day 7, median scores improved by 40%, 79%, and 68%, respectively ($P<.001$). By day 14, median scores improved by 60%, 79%, and 76%, respectively ($P<.001$).

By day 3, participants rated their disease severity using the SGA as having moderate improvement (median, 3.0; mean, 2.9; 95% CI, 2.3-3.5). By day 14, participants rated their disease severity as having marked improvement (median, 2.0; mean, 2.4; 95% CI, 1.7-3.2).

By the end of the study period, 11 of 20 participants achieved an IGA rating of clear or almost clear. Eight of 20 participants had at least a 75% improvement in EASI scores by day 14. The magnitude of improvement in EASI scores positively correlated with the baseline EASI ($P<.001$) (Figure 5). Six of 18 participants rated their skin as clear or almost clear on the SGA by day 14. For the investigator global assessment of response to treatment, 3 participants were rated as clear or almost clear by day 3, while 8 participants were rated clear or almost clear by day 14.

Two adverse events reported during the study period were determined by investigators to be unrelated to treatment, including nausea and a carbuncle on the buttock of a participant; both were mild and resolved. No serious adverse events were reported.

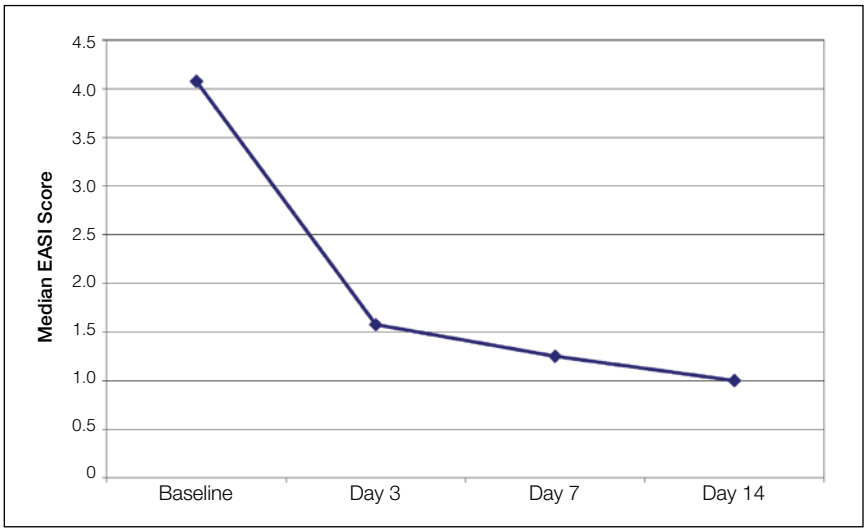

Figure 4. Improvement in median eczema area and severity index (EASI) scores over time (scale of 0–72; higher number indicates worse disease). There was significant improvement from baseline for each time point ($P<.001$).

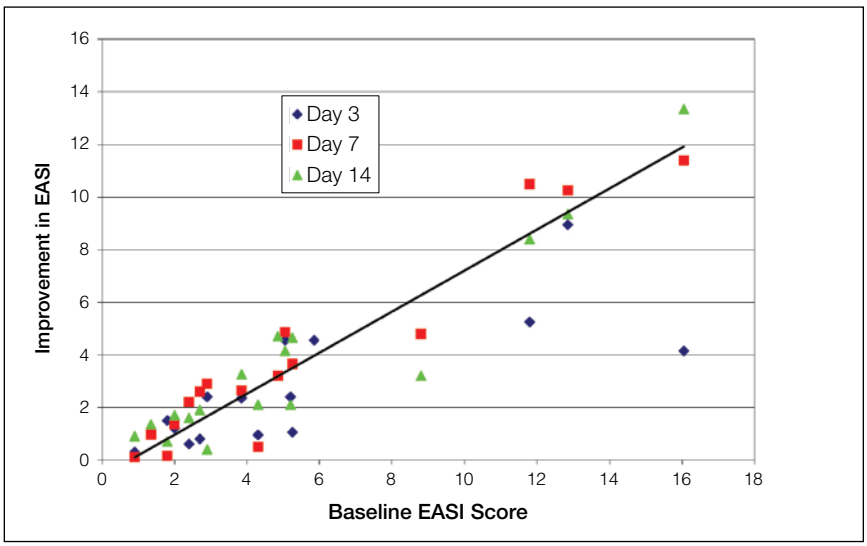

Figure 5. The magnitude of improvement in atopic dermatitis correlated with baseline severity. Three days of fluocinonide cream 0.1% is effective for mild to severe disease. Participants with more severe disease (higher eczema area and severity index [EASI] scores [scale of 0–72]) at baseline also had a larger magnitude of improvement in disease severity by the end of the study ($P<.001$). Solid line indicates linear trend.

Comment

Results of this study revealed that a 3-day treatment course was associated with far better adherence compared to the observations of Krejci-Manwaring et al[4] in an earlier 8-week study in which there was a 60% drop in adherence over the first 3 days. The level of adherence in this short study was higher than several other atopic dermatitis studies,[11,12] with all participants applying the medications at least once daily. We believe the short treatment interval contributed to good adherence in this population through a white coat compliance effect and reduced apparent burden of treatment.

Surprisingly, the mean adherence in this study was less than 100%. Other factors (eg, fear of side effects, vehicle preferences, perceived efficacy of treatment) clearly play a role in the noncompliance of some patients. Future studies explaining why patients are more adherent to this short treatment interval (eg, less burdensome treatment, greater sense of self-efficacy, less fear of side effects) would help guide the development of adherence interventions. Although additional systems are needed to ensure perfect adherence to treatment, the use of a short initial treatment period may be a feasible approach to promote better adherence to topical corticosteroid therapy in actual practice.

The white coat compliance phenomenon can be used to the physician's advantage and a follow-up visit shortly after beginning treatment can encourage consistent medication use. Good adherence can translate to rapid disease improvement. By providing patients proof of efficacy early in the treatment, they may subsequently have a greater willingness to continue to faithfully apply the medication.[9] While frequent follow-up visits throughout the duration of a patient's care would likely increase levels of adherence and improve clinical outcomes, it is an impractical

solution due to time and cost constraints. However, even 1 visit that promotes good early adherence and better outcomes could potentially have long-term benefits by increasing patient trust in and use of the medication.

Improvement in disease severity was seen as early as the third day of this study, and even though the topical therapy was discontinued on day 2 or day 3, disease severity continued to improve through the end of the 14-day study. Although the small sample size is a limitation of the study, the magnitude of improvement was sufficiently large enough to be detectable and significant. The observed degree of efficacy is likely a result of excellent adherence. However, overall skin care regimens, including liberal use of nonmedicated moisturizers and gentle soaps, are essential in patients with atopic dermatitis to help control the recurrence of inflammation and pruritus as well as to repair the skin's barrier function.

A limitation of the electronic monitoring used in this study is that the data do not quantify the amount of applied medication. Although it is possible that patients opened the cap and did not use the medication, this behavior seems unlikely considering the observed improvement in atopic dermatitis severity. The open-label design precludes knowing how much benefit was due to the treatment, though it seems unlikely that there would be a high frequency of spontaneous disease improvement over the short treatment interval. Because only 1 participant had severe disease (defined by the IGA) in the study, conclusions about effectiveness of the treatment in patients with severe atopic dermatitis are limited. The small sample size prevents any meaningful subset analysis of other correlations, such as age and adherence or the amount of disease improvement and adherence. Furthermore, the 2 participants that were lost to follow-up may represent additional noncompliance and illustrates the need for more research on additional influences on patient use of the medication.

For patients with unresponsive or minimally improved atopic dermatitis, nonadherence to topical corticosteroid treatment should be suspected before recalcitrant disease is presumed. Many factors play a role in nonadherence to treatment and barriers to daily applications should be sought out by physicians rather than immediately switching to other therapies. Although this study provides information about short-term treatment, the short-term nature of the study precludes analysis of long-term effects. The effect of visit strategies to promote better long-term treatment outcomes (both efficacy and safety outcomes) should be explored.

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