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Commentary

Adherence to a five day treatment course of topical fluocinonide 0.1% cream in atopic dermatitis

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Abstract

Background: Adherence in the treatment of chronic inflammatory skin diseases such as atopic dermatitis is poor. Methods to improve adherence have proven difficult.

Purpose: To determine whether a short course of treatment with a high-potency corticosteroid will improve adherence compared to longer treatment studies and if improvement in disease and itch continues after treatment.

Methods: 10 patients with mild to moderate atopic dermatitis were instructed to apply fluocinonide 0.1% cream twice daily for 5 days. Adherence was self-reported and electronically monitored. Treatment outcomes were assessed in terms of Visual Analog Scale of Itch (VAS), Eczema Area and Severity Index (EASI), and Investigator Global Assessment (IGA) scores.

Results: The median adherence rate was 40% (range of 0-100). The median percent change in VAS from baseline measures on days 7 and 14 were 90% (range -13, 100, p=0.02) and 52% (range 0, 100, p=0.004). On days 7 and 14, 20% and 70% patients achieved an EASI-75 and 40% and 60% an IGA of 0 or 1.

Limitations: Small sample size limited subgroup analyses.

Conclusions: Adherence rates with short-term treatment were similar to previously reported rates in longer term treatment studies. However, even non-adherent patients had significant improvement in itch and disease severity.

Keywords: adherence, chronic inflammatory diseases, atopic dermatitis, fluocinonide, MEMS cap

Introduction

Atopic dermatitis (AD) is one of the most prevalent skin diseases in the U.S. population today, affecting an estimated 17.8 million people [1]. Whereas AD classically presents within the first few years of life, it often persists into adulthood [2]. This chronic condition presents with erythematous, scaly, and extremely pruritic skin. The mainstay of treatment is topical corticosteroids because of their ability to reduce inflammation and erythema – reducing itch and disrupting the itch-scratch cycle. The recurring and remitting nature of the disease requires long term treatment regimens with topical corticosteroids.

A chronic condition, AD requires treatment over extended periods of time. Topical corticosteroids are highly effective treatments, but the effectiveness of treatment is limited by poor adherence, even in patients with symptomatically active disease. Adherence to treatment affects outcomes of chronic disease. However, more empirical evidence is needed concerning adherence in chronic conditions treated with topical therapy, like AD [3]. The use of electronic monitoring devices reveals that self reported adherence is not a reliable measure of actual adherence. A pilot study in ten adult subjects with psoriasis showed that 26% of self reported doses on medication use logs were not verified by electronic monitors [4]. Similarly, adherence rates to topical therapy in an 8 week psoriasis study was 55% according to MEMS cap data compared to the 90-100% adherence rates reported by medication diaries [5]. Poor adherence appears to be multifactorial, with frustration with medication efficacy, inconvenience of treatment regimes, and fear of side effects cited as important barriers to proper use [6]. In the pediatric population, cost and concerns about safety of the prescribed medication are barriers to treatment in chronic inflammatory skin diseases including AD [7]. A strong physician-patient relationship that focuses on trust, patent education, and patient preferences regarding treatment plan have been recommended strategies to help improve adherence and ultimately improve outcomes [8].

Whereas long-term treatment with topical corticosteroids is an effective therapy for atopic dermatitis, a short course of a high potency strength topical steroid may also reduce the severity of disease. Because patient adherence is problematic in chronic diseases, a short five day course of a topical corticosteroid may allow for better patient adherence than a longer treatment course, as has been previously reported in AD patients treated with topical fluocinonide cream for 3 days [9]. Also, improvement in disease and itch may continue to be evident after this short-term course is completed.

The purpose of this study is to determine whether a shorter treatment course will improve adherence compared to previously reported adherence in longer treatment courses and whether a few extra days of treatment will impact adherence and treatment outcomes compared to a shorter 3 day treatment course. We will assess the tolerability and efficacy of short-term treatment with a high potency topical corticosteroid, fluocinonide cream 0.1%, in the treatment of atopic dermatitis.

Methods

This was a single center, prospective, open label study of fluocinonide cream 0.1% (Vanos®) for the treatment of children and adults with mild to severe atopic dermatitis. A score of 2 to 4 on the Investigator Global Assessment scale and a score greater than or equal to 50 on the 100-point Visual Analog Scale of Itch was required for subject enrollment. Ten subjects aged 12 and above were recruited from the Dermatology Clinic at Wake Forest School of Medicine and were enrolled after informed consent was obtained. Subjects were not allowed to use other prescription therapies for the treatment of AD during the course of the study, systemic anti-inflammatory medications within 4 weeks of baseline, or topical corticosteroids within 2 weeks of baseline. Also excluded were: subjects with a known allergy or sensitivity to fluocinonide cream or its components, pregnant or breastfeeding subjects, and those with disease involvement requiring more than 60 grams of cream in a 1 week period. Approval for this study was obtained from Wake Forest School of Medicine Institutional Review Board.

At baseline (visit 1), the diagnosis of AD was confirmed by the investigator. Severity of disease was then assessed using the Investigator Global Assessment (IGA) scale, the Eczema Area and Severity Index (EASI), and body surface area (BSA) involvement. Subjects then completed the Subject Global Assessment (SGA) questionnaire and the Visual Analog Scale of Itch (VAS). Subjects were also instructed to fill out the VAS for each of the first 7 days of the study. A tube of fluocinonide cream 0.1% , fitted with a Medication Event Monitoring System (MEMS®, AARDEX Group Ltd., Sion, Switzerland), was given with instructions to apply the medication twice daily beginning on day 2 of the study. Patients were not told adherence would be monitored through the use of an electronic monitoring device. A medication diary was provided and subjects were asked to record when they used the medication. A target lesion most representative of the overall disease was chosen and 4 photographs were taken, two photos 12 to 18 inches away from the subject and two photos 24 to 30 inches away.

At day 7 or 8 (visit 2), severity of disease was assessed using the IGA, EASI, BSA, and Investigator Global Assessment of Improvement. Subjects again completed the SGA and VAS at this visit. The take home VAS, medication diary, and study medication were collected. The MEMS® cap data was downloaded using PowerView software (AARDEX).

At day 14 (visit 3), severity of disease was again assessed using the IGA, EASI, BSA, and Investigator Global Assessment of Improvement. Subjects completed the SGA and VAS. Four photographs of the same target lesion were repeated in the same manner as visit 1. Subjects were informed at this final visit of the adherence monitoring and individualized adherence behaviors were discussed.

The primary endpoint of this study was the reduction in atopic dermatitis severity from baseline to day 7 after using fluocinonide cream 0.1% for 5 days. Reduction in severity of disease from baseline was quantified using the Investigator Global Assessment scale. Other secondary endpoints included: Investigator Global Assessment measuring reduction in AD severity from Baseline to

day 14, reduction in EASI score, BSA involvement, and Investigator Global Assessment of Improvement from baseline to day 7 and from baseline to day 14.

Subjective assessment of AD was measured using the Subject Global Assessment and Visual Analog Scale of Itch. Adherence was measured using MEMS cap data; average daily adherence during the treatment phase (from day 2 to day 7) compared to published sources was assessed.

Median percent changes in the VAS and EASI scores at days 7 and 14 were assessed using the Sign test. Proportions of patients receiving an IGA score of 0 or 1 or a 75% or greater reduction in the EASI score were reported for each follow-up visit period. Adherence rates were defined as the daily adherence and cumulative dose adherence. Daily adherence was defined as the number of days a patient took the correct number of prescribed doses divided by the total number of days the medication was prescribed. Cumulative dose adherence was defined as the total number of doses taken divided by the total number of doses prescribed. For any days on which the number of doses used exceeded the 2 prescribed doses, the doses were entered as 2 and patients were considered adherent on that day. The Sign test was also used to compare adherence rates reported in diaries versus those recorded with the electronic MEMS caps. Categorical variables were compared using Fisher's exact test. Data were analyzed with a complete-case analysis method. All analyses were performed using SAS 9.2 (SAS Institute Inc.; Cary, NC).

Results

Ten subjects with atopic dermatitis completed the study. All ten subjects completed both follow-up visits. One MEMS cap malfunctioned, so electronic adherence data was only available for nine subjects. The majority of the patients, 7 out of 10, were female, with a median age of 25 (range 14-65). Six of the patients were white and four patients were black. The median percent change in VAS from baseline measures on day 7, after 5 days of treatment, was 90% (range -13, 100, p=0.02) and on day 14, one week after completing treatment, was 52% (range 0, 100, p=0.004). The median percent change in EASI on day 7 was 54% (range 27, 79, p=0.002) and on day 14 was 80% (range -5, 99, p=0.02) (Table 1). On day 7, after 5 days of treatment, 20% (2 out of 10) patients had achieved an EASI-75 and 40% (4/10) had an IGA of 0 or 1. On day 14, one week after completing treatment, 70% (7/10) patients had achieved at least an EASI-75 and 60% (6/10) had an IGA of 0 or 1. Regardless of total doses taken, most patients had high percent changes in their VAS and EASI scores by the second week of the study (Figure 1).

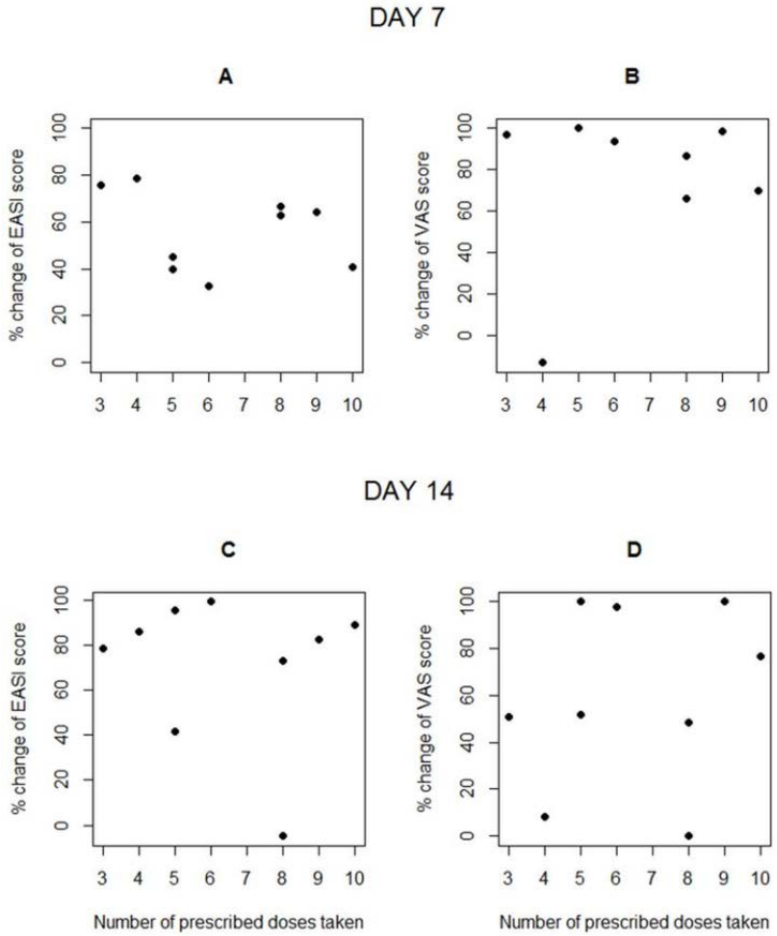

Figure 1. Percent change EASI and VAS scores and adherence. Percent changes in EASI and VAS scores from baseline to day 7 (A & B) and day 14 (1 week after completed treatment, C & D) based on the total number of prescribed doses taken by a patient. For patients with more than two medication applications per day, the total usage was rounded down to two applications.

The median daily adherence rate for the 5 days of treatment was 40%, with a range of 0-100%. The median adherence rate based on the patients' medication diary was 100%, with a range of 80-100%. Better adherence was seen on day 1 of treatment on which 6 out of 9 of the patients were adherent compared to day 5 on which only 1 out of 9 patient was adherent (Figure 2). The cumulative dose median adherence rate was 60% (range 30-100%) compared to the medication diary median adherence of 100% (range 90-100%, p=0.008).

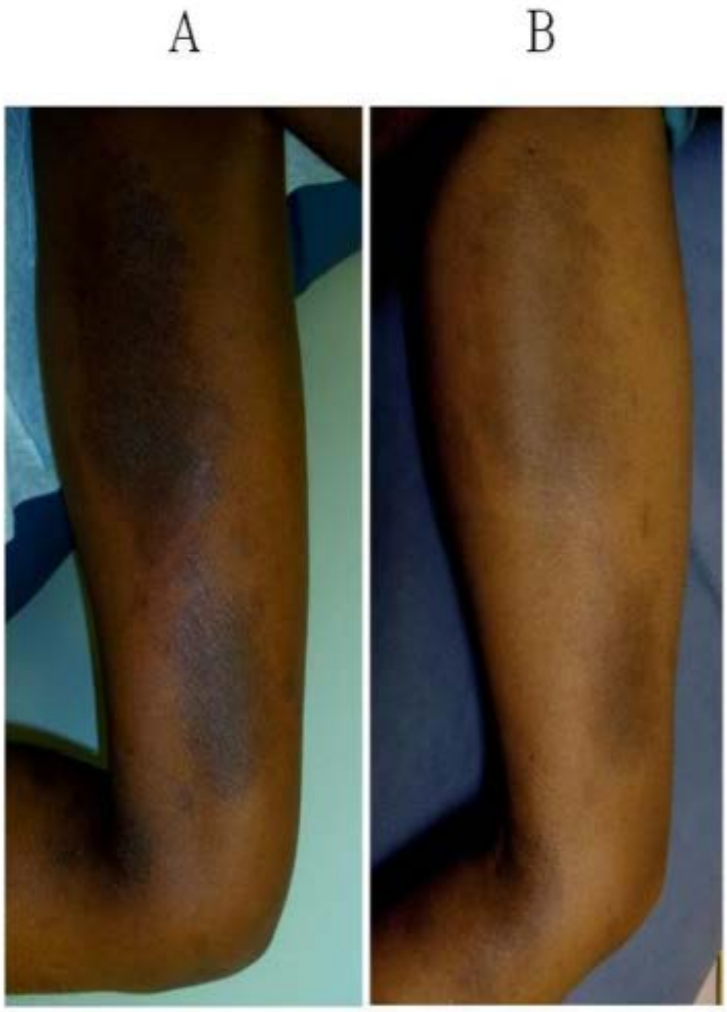

Figure 2. Atopic Dermatitis. Improvement in active disease in a patient with cumulative dose adherence rate of 50%. Patient with atopic dermatitis at baseline prior to treatment (A). Same patient at day 7 after treatment with topical fluocinonide 0.1% cream once daily (B).

Four of the nine patients applied the medication at least once per day every day. Using Fisher's exact test, there was no difference between patients that applied mediation at least once every day compared to patients that missed applications for some days in the likelihood of having a clear or almost clear IGA score by day 7 (p=0.57) or day 14 (p=0.08). Similarly, there was no association between using at least one application per day and the number of subjects that achieved EASI-75 (p=0.47) or VAS-75 (p=0.57) at day 7. However, at day 14, the association was significant for VAS-75 (p=0.005) and borderline non-significant for EASI-75 (p=0.08).

Three out of nine patients applied the medication more than twice on at least one day. There was no difference between these patients and patients that used the medication twice or less a day in the change in IGA score (day 14 p=0.42), or in the percent change in EASI (day 7 p=0.99; day 14 p=0.71), VASI (day 7 p=0.54; day 14 p=0.39), or BSA (day 7 and day 14 p>0.999) at day 7 or day 14. In addition, there was no statistically significant difference between the two groups in whether they had sustained improvement, defined as the change in outcome measures between day 7 and day 14, at the end of the study (EASI p>0.99; VASI p=0.54; BSA>0.99) (Figure 3).

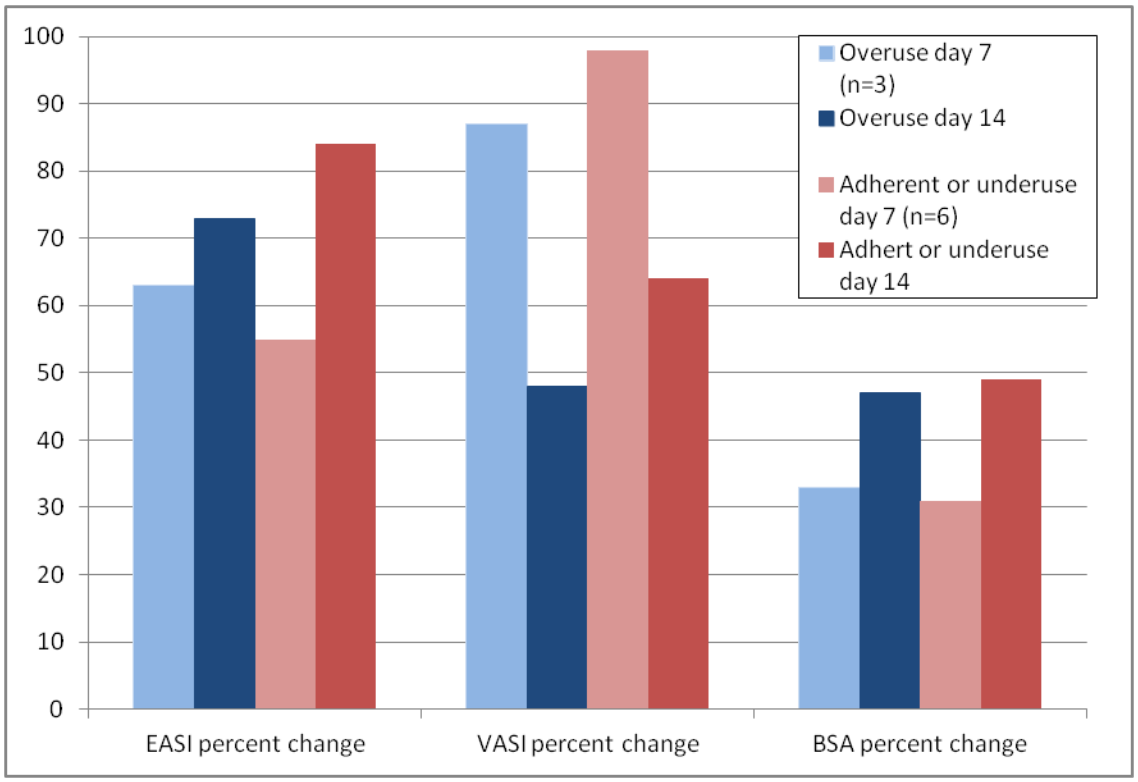

Figure 3. Outcome measures for patients that overused medication. Percent changes in EASI, VASI, and BSA scores for patients that applied medication more than twice daily for at least one day (overuse) compared to patients that applied the medication twice or less daily (adherent or underuse). P>0.05 for changes in all outcome measures

Discussion

Poor adherence is an acknowledged obstacle in the treatment of chronic skin diseases. Attempts to improve adherence have proven difficult. In the treatment of acne the use of customized text messages or a daily phone call to patients reminding them to use their medication was not an effective means of improving adherence [10,11]. Increasing the frequency of office visits in acne has improved adherence; although not statistically significant, a similar finding was seen in AD [10,12]. In this study, a short treatment course with a topical corticosteroid had a median rate of 40% similar to previously reported rates of 32-55% based on MEMS cap data [5,13]. This differs from previous reports of improved adherence with short term treatment. Median adherence rate for AD patients treated for 3 days with fluocinonide 0.1% cream was 100% [9]. However, as demonstrated by the significant improvements in the EASI and VAS scores, even patients who were not adherent and applied less medication than prescribed saw significant improvements in itch and disease severity (Figure 3). There was no difference between patients that applied mediation at least once every day compared to patients that missed applications for some days in the likelihood of having a clear or almost clear IGA score or in achieving a VAS-75 or EASI-75 at day 7. So despite less than ideal adherence, patients improved and this improvement occurred quickly, within 5 days or less of treatment. Furthermore, improvement over baseline in EASI, IGA, and VAS continued for a least one week after treatment was completed. The patients that used the topical steroid at least once daily for the 5 days of treatment were more likely to have VAS-75 at day 14 than patients who did not use the medication at least once daily. Using the medication more often than prescribed (more than twice daily) at least once during the treatment period did not result in greater improvement in any of the outcome measures at day 7 or day 14 compared to using the medication as prescribed (twice daily) or less. This provides evidence that a short term course of treatment with topical fluocinonide 0.1% cream is effective for treatment of active disease, with therapeutic effects continuing beyond the treatment period. Additionally, this improvement in disease that continues even after treatment is complete is more significant in terms of achieving VAS-75 in patients that were more adherent to the treatment regimen.

Many studies assessing adherence to treatment rely on self reported medication use, which is an unreliable method [4,5]. Adherence rates based on self reported medication diaries differed significantly compared to actual adherence rates based on MEMS cap data, median of 100% versus 40%. Not only do patients over-report use of medication, they also under-report their use. Whereas this may be the result of patients' desire to strictly comply with instructions in the setting of a study, the under-reporting of medication use may provide some insight into adherence behaviors. Overall it further supports the need for monitoring methods beyond self reporting to adequately assess true adherence in the treatment of chronic skin diseases.

The small sample size of this study limited most subgroup analyses. A larger study may provide evidence that better adherence does result in better treatment outcomes. However, despite a small sample size, the results from this study showing patients had significant improvement in disease with topical fluocinonide was statically significant.

There are different rationales behind the use of topical corticosteroids in the treatment of chronic inflammatory diseases. The well accepted approach of using the lowest potency steroid necessary to effectively treat the disease is often preferred, with the thought that this route avoids potential side effects. Another approach is to start treatment with a high potency topical steroid treating the disease aggressively, but limit treatment to a short duration to avoid potential side effects. This method of burst treatment with a high potency steroid is as effective as longer treatment with a milder steroid [14]. Since adherence to topical medication use has been difficult to modify, and given that patients show significant improvement despite poor adherence when using a high potency topical steroid, the second approach may be a good choice for patients with AD that appears "resistant" to topical corticosteroids because resistance may be mediated by poor adherence.

Table 1. Median percent change in VAS and EASI scores.

	Median Percent Change in Measure (Range)	**p-value**
Day 7		
VAS	90 (-13, 100)	0.02
EASI	54 (27, 79)	0.002
Day 14		
VAS	52 (0, 100)	0.004
EASI	80 (-5, 99)	0.02

Table 1. Median percent change in VAS and EASI scores. Percent change calculated as the difference of the baseline score from the given week's score, standardized by the baseline score. This measure was then assessed using the Sign Test to see if the change was different from 0 (suggesting no change in score).

Table 2. Actual adherence compared to self-reported adherence from medication diaries.

	DAY				
Subject	1	2	3	4	5
2	4	2	2	2	0
3	2	1	0	2	0
4	2	2	2	2	2
5	1	1	1	1	1
6	1	1	1*	1	0
7	1	1	1	0	0
8	3	1	1	1	1
9	2	2	2	2	1
10	6	2	3	2	0

Table 2. Actual adherence compared to self-reported adherence from medication diaries. All patients reported applying their medication twice daily in their journals, except for patient 6 on day 3. *Patient 6 reported only applying the medication 1 time on day 3. Numbers in the cells represent the MEMS values recorded for a given day. Green= when journal entries match MEMS data. Red= when the patient took no medication. Yellow= when a patient used less than the prescribed dose of the medication. Dark green= when the patient took more than the prescribed dose of medication.

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