

Antipruritic Hydrogel for the Treatment of Atopic Dermatitis: An Open-Label Pilot Study

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Atopic dermatitis (AD) is the most common chronic inflammatory skin disease in industrialized nations. The efficacy and tolerability of Atrapro (RD047-26) antipruritic hydrogel was evaluated in 17 adult participants with mild to moderate AD with associated pruritus. The antipruritic hydrogel was applied 3 times daily to the affected areas of the body, and participants were evaluated on days 3, 7, and 14 (end of study). There were 3 efficacy end points: investigator global assessment (IGA), investigator pruritus assessment (IPA), and participant itch assessment (PIA). All 3 efficacy end points were met and showed a statistically significant improvement in the mean score from baseline to day 14 ($P < .001$). The mean IGA score improved 43% from a baseline score of 2.7 to a day 14 score of 1.53 ($P < .001$) on a 5-point scale (0 = clear; 4 = severe). The severity of pruritus decreased in 88% (15/17) of participants from baseline to day 14 based on the IPA and 82% (14/17) of participants based on the PIA. Most participants (82% [14/17]) experienced relief from itching by day 3, and this improvement remained consistent at each of the follow-up office visits. The only adverse event (AE) was mild postapplication skin dryness, which was reported by 59% (10/17) of participants and resolved with increased use of emollients. Based on these

promising results, further research on the antipruritic hydrogel is warranted.

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Atopic dermatitis (AD) is a chronic inflammatory skin disease that affects up to 30% of children and 10% of adults worldwide.¹ Variations in immunologic responses and genetic susceptibility predispose some individuals to AD, and defects in epithelial barrier function allow increased staphylococcal skin colonization.^{2,3} The clinical symptoms of AD include pruritus, erythema, and excoriations, followed by colonization with *Staphylococcus aureus*, which has been demonstrated in more than 90% of AD lesions.³

Short-term treatment of AD typically involves the use of topical corticosteroids, which effectively alleviate pruritus and excoriations, but long-term use may result in irritation, discoloration, or thinning of the skin, and may increase the risk for infection.⁴ Topical antimicrobial agents frequently are used to decrease the bacterial count and help prevent future disease flare.⁵ The most common antimicrobial agents used that contain triclosan or chlorhexidine have shown effectiveness in the reduction of *Staphylococcus* numbers; however, the level of effectiveness is not substantial enough to improve the overall AD severity scores, and these antiseptic agents have not demonstrated benefits over the use of anti-inflammatory products.⁵ Consequently, the use of these agents may not be warranted due to the potential for systemic toxicity with triclosan^{5,7} as well as severe allergic reaction with triclosan^{5,8,9} and chlorhexidine.^{5,10-12}

Restoration of epidermal barrier function ultimately is the goal in the treatment of AD. Atrapro (RD047-26) antipruritic hydrogel is a novel topical treatment that was developed to address the

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challenges of AD. The formulation was designed to promote moisture retention and reduce itching, pain, and burning. It is a colorless, nonoily, pH-neutral, emollient-containing gel that is comprised of oxychlorine compounds, specifically hypochlorous acid and sodium hypochlorite. The safety and efficacy of this antipruritic hydrogel was evaluated for the treatment of mild to moderate AD in an open-label, single-center pilot study.

Methods

The study protocol was approved by an institutional review board. All participants provided informed consent. The study was conducted according to the Good Clinical Practice guidelines of the International Conference on Harmonisation, the Declaration of Helsinki, and applicable federal and local regulatory requirements.

Participants—Male and female adults (aged 18–65 years) were enrolled if they were in good general health; if they had AD as defined by the AD criteria set forth by Hanifin and Rajka,¹³ including a minimum of 3 major and 3 minor symptoms; if they had AD patches covering 5% to 25% of their body surface area (BSA); if they had mild to moderate AD based on an investigator global assessment (IGA) rating of 2 (mild) or 3 (moderate)(Table 1)¹⁴; and if they had AD with associated pruritus based on an investigator pruritus assessment (IPA) score of 2 (moderate) (Table 2).¹⁵ Participants were required to use the same type of skin and hair products including soaps, moisturizers, lotions, creams, ointments, sunscreens, and shampoos for a minimum of 2 weeks prior to baseline, and continue to use the same products with a similar frequency throughout the study. Women of childbearing potential had to have a negative urine pregnancy test at baseline and use an effective method of birth control throughout the study.

Participants were excluded if they had a history of allergy or sensitivity to any of the components of the investigational product; had severe or uncontrolled asthma; had an anticipated need for surgery or hospitalization during the study; were pregnant, nursing, or planning a pregnancy during the study; were enrolled in a subsequent investigational drug or device study during the study; or were enrolled in an investigational drug or device study within 30 days prior to baseline.

Treatment—Treatment consisted of topical application of Atrapro antipruritic hydrogel. The first application to the affected areas of the body was done by the investigator at the baseline (day 0) office visit. At this visit the participant was trained on the application of the antipruritic hydrogel and was instructed to apply it to affected areas 3 times daily at least

Table 1.

Investigator Global Assessment

Score	Category	Description
0	Clear	No signs of inflammatory atopic dermatitis
1	Almost clear	Faint, barely detectable erythema and/or trace residual elevation in limited areas; neither excoriation nor oozing/crusting are present
2	Mild	Light pink erythema and slightly perceptible elevation; excoriation, if present, is mild
3	Moderate	Dull red, clearly distinguishable erythema and clearly perceptible elevation but not extensive; if present, excoriation or oozing/crusting are mild to moderate
4	Severe	Deep/dark red erythema and marked and extensive elevation; excoriation and oozing/crusting are present

Data from Yentzer et al.¹⁴

3 hours apart for 2 weeks. Participants also received instructions on how to complete a daily diary.

End Points—Efficacy was measured according to 3 instruments, which were completed at each office visit (baseline and days 3, 7, and 14). The investigator visually assessed the overall severity of a participant's AD based on the IGA (Table 1).¹⁴ The investigator assessed the participant's pruritus, scratching, and discomfort a few days prior to the baseline office visit based on the IPA (Table 2).¹⁵ Additionally, participants self-reported the severity of itching a few days prior to the baseline office visit using the participant itch assessment (PIA).¹⁴ The PIA is a visual analog scale that ranges from no itch to worst

Table 2.

Investigator Pruritus Assessment

Score	Category	Description
0	None	None
1	Mild	Occasional slight itching/scratching
2	Moderate	Constant or intermittent itching/scratching/discomfort, which may occasionally disturb sleep
3	Severe	Bothersome itching/scratching/discomfort, which definitely disturbs sleep

Data from Fujita et al.¹⁵

itch imaginable. The PIA scores were normalized to a scale of 1 (no itch) to 10 (worst itch imaginable). The total BSA affected by AD and the treated BSA also were measured at each office visit based on the percentage of the head and neck, upper limbs, trunk, and lower limbs affected by AD and treated for AD, respectively.

Safety was evaluated at each office visit (baseline and days 3, 7, and 14). Adverse events (AEs) were graded based on the CTEP (cancer therapy evaluation program) CTCAE (common terminology criteria for AEs) version 4.02, if applicable, or as mild (grade 1), moderate (grade 2), severe (grade 3), or life threatening (grade 4). The relationship of AEs to the treatment was assessed by the investigator as unrelated, unlikely, possible, probable, or definite.

Statistical Analysis—All statistical programming was performed using SAS version 9.1 or higher. Statistical significance was based on 2-tailed tests at the 5% level of significance ($P < .05$). Analysis of the mean change (reduction) from baseline on the 3 efficacy assessment scales (IGA, IPA, and PIA) was based on a paired t test.

Results

Demographics—Of the 17 patients who were screened, enrolled, and treated, all 17 completed the study. The majority of participants were black women aged 28 to 56 years (Table 3).

Table 3.

Demographics at Baseline

Demographics	Participants
No. of participants	17
Mean age, y (range)	46 (28–56)
Sex	
Female, n (%)	15 (88)
Male, n (%)	2 (12)
Race	
Black, n (%)	12 (71)
White	5 (29)
Mean IGA score ^a (range)	2.7 (2–3)
Mean IPA score ^b (range)	2.3 (2–3)
Mean PIA score ^c (range)	6.9 (3–9)

Abbreviations: IGA, investigator global assessment; IPA, investigator pruritus assessment; PIA, participant itch assessment.

^aScored as 0 (clear), 1 (almost clear), 2 (mild), 3 (moderate), or 4 (severe).¹⁴^bScored as 0 (none), 1 (mild), 2 (moderate), or 3 (severe).¹⁵^cScored as 1 (no itch) to 10 (worst itch imaginable).¹⁴

Efficacy Assessments—The percentage of participants with a reduction based on the IGA steadily increased from baseline to day 14 (Figure 1). The mean IGA score showed significant improvement (43%) from a baseline score of 2.7 to a day 14 score of 1.53 based on a 5-point scale ($P < .001$). Of the 5 participants with mild AD (IGA score of 2) at baseline, 4 (80%) were rated on the IGA scale as clear (score of 0) or almost clear (score of 1) at day 14. Of the 12 participants with moderate AD (IGA score of 3) at baseline, 4 (33%) were rated as clear or almost clear at day 14.

The percentage of participants with a reduction in pruritus based on the IPA also increased from baseline to day 14 (Figure 2). The mean IPA score showed significant improvement (44%) from a baseline score of 2.3 to a day 14 score of 1.29 based on a 4-point scale ($P < .001$). The PIA also demonstrated relief from itching with a 39% improvement from baseline. Most participants (82% [14/17]) experienced rapid itch relief by day 3 and the reduction of pruritus remained constant throughout the study. The mean

change (reduction) based on the PIA from baseline was statistically significant at each evaluation ($P < .001$) (Figure 3). When participants were categorized by race, the mean scores in the IGA, IPA, and PIA scales at baseline and day 14 were not significantly different between groups.

The proportion of participants who experienced a reduction in the percentage of BSA affected by AD had increased at each evaluation to 65% (11/17) of participants by day 14. The mean reduction from baseline to day 14 in participants' BSA affected by AD was 37% ($P < .001$).

Safety Assessments—Ten participants (59%) had treatment-related AEs of postapplication skin dryness; however, all of the AEs were mild and had resolved with increased use of the emollient the participants were using at the beginning of the study and had continued to use throughout the study. Efficacy results were similar between the group of participants with postapplication dryness and those in the group with no AEs.

Comment

Atopic dermatitis encompasses a broad spectrum of symptoms and is the most common chronic inflammatory skin disease in industrialized nations. Atopic dermatitis affects individuals of all races and is more common in individuals who live in cold climates, urban settings, and developed countries.¹⁶ Although AD is more common in children, adult-onset AD typically presents in early adulthood and occurs more often in women.¹⁷ This study was carried out

in the United States in a metropolitan area with a population exceeding 1.6 million individuals. The participants selected for this study were adults and mostly women. The study population represented the midrange of the AD population consisting of patients experiencing mild to moderate disease with

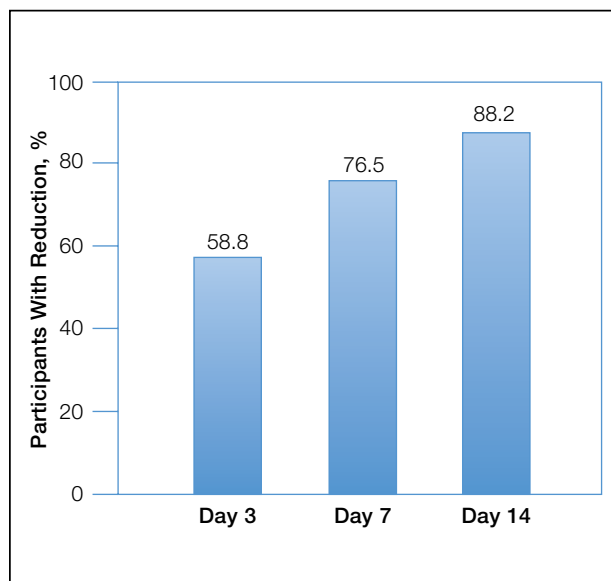


Figure 2. Percentage of participants with a reduction from baseline on the investigator pruritus assessment (N=17).

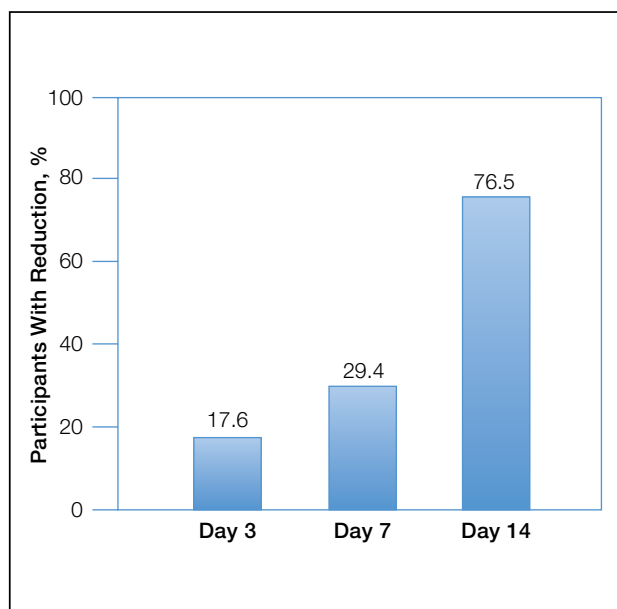


Figure 1. Percentage of participants with a reduction from baseline on the investigator global assessment (N=17).

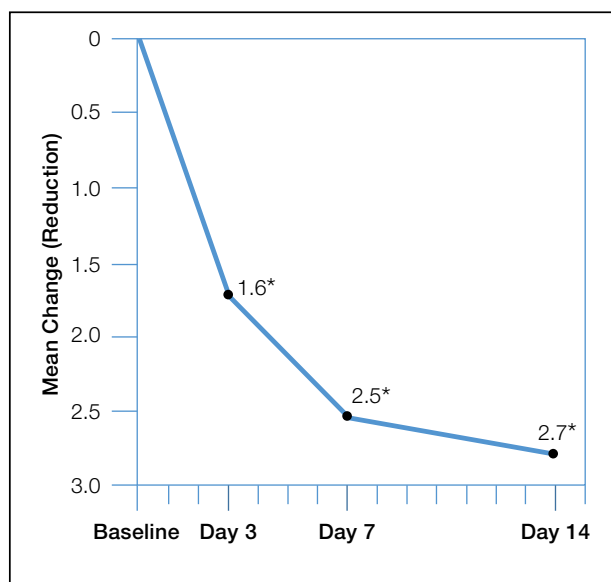


Figure 3. Mean change (reduction) in pruritus from baseline to days 3, 7, and 14 for the participant itch assessment. Asterisk indicates $P < .001$.

pruritus. All of the participants had a history of AD and felt that their current treatment was not sufficient in controlling their condition. The majority of the participants generally responded to treatment with the antipruritic hydrogel by day 3 and continued to respond for the duration of the 14-day study phase. Response was defined as a reduction in disease severity as well as a reduction in the severity of pruritus, with the latter end point independently evaluated by the investigator and the participant. All 3 end points were met and the mean change (reduction) from baseline was significant for the 3 end points ($P < .001$). In addition, a significant reduction in the percentage of affected BSA was observed at the end of the study ($P < .001$).

Numerous instruments exist to measure the severity and response to treatment of AD. The instruments used in this study included a global assessment of the severity of disease as assessed by the investigator, a specific assessment of pruritus as evaluated by the investigator, and an assessment of pruritus from the perspective of the participant. The results of the participant's assessment of pruritus were consistent with the investigator's assessment at each of the 3 follow-up office visits. Participants were seen by the investigator at days 3, 7, and 14 to evaluate the onset of response and the consistency of the response over time. In prior reports, patient adherence to AD treatment had been shown to drop following the first treatment and increase before an upcoming office visit.^{14,18,19} The frequency of office visits and short intervals between the first treatment and the first office visit may have improved compliance in this study. In addition to office evaluations, participants completed a daily diary that demonstrated remarkable compliance with the treatment regimen, which consisted of the application of the antipruritic hydrogel 3 times daily to the affected areas. This compliance suggested that these participants with AD were highly motivated to improve their disease, which also may be the case with the general population of patients with AD and associated pruritus. In addition, the colorless, water-based qualities of the antipruritic hydrogel rendered the treatment easy for participants to apply without the concern of a greasy feeling, an oily or discolored appearance, or a detrimental effect on their clothing.

Yentzer et al¹⁴ showed a similar high level of compliance in a study of AD treatment that also included office visits on days 3, 7, and 14, in addition to electronic monitoring. In the study, approximately 55% (11/20) of participants with mild to moderate AD achieved an IGA score of clear or almost clear following corticosteroid therapy with fluocinonide cream 0.1%,¹⁴ which is similar to the results of the antipruritic hydrogel treatment used in the present

study in which 47% (8/17) of participants were clear or almost clear at day 14.

The main goal of this study was to assess if the antipruritic hydrogel improved the pruritus associated with AD. The secondary goal was to determine if the antipruritic hydrogel had an effect on the overall AD present at baseline. All 3 primary end points were met and the treatment was well-tolerated. This study was limited by the small population size and by the lack of a control group. There was no washout period that allowed us to assess the effects of an additional treatment added to the participant's standard of care as opposed to the effects of the treatment alone. The study included 3 follow-up visits over a 2-week study phase, which allowed us to assess the time course of the response.

The favorable results of this study support further research of the use of the antipruritic hydrogel as an alternative treatment of AD compared with standard topical therapies. In addition, the use of the antipruritic hydrogel may potentially eliminate or decrease the need for systemic therapy.

Conclusion

In this open-label, single-center pilot study, the antipruritic hydrogel appeared to be a well-tolerated and effective treatment of AD. A significant reduction in pruritus was observed by the investigator ($P < .001$) as well as approximately 90% of participants.

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REFERENCES

1. Bieber T. Atopic dermatitis [published online ahead of print May 17, 2010]. *Ann Dermatol*. 2010;22:125-137.
2. Bieber T. Atopic dermatitis. *N Engl J Med*. 2008;358:1483-1494.
3. Beltrani VS, Boguniewicz M. Atopic dermatitis. *Dermatol Online J*. 2003;9:1.
4. Bruner CR, Feldman SR, Ventrappagada M, et al. A systematic review of adverse effects associated with topical treatments for psoriasis. *Dermatol Online J*. 2003;9:2.
5. Schnopp C, Ring J, Mempel M. The role of antibacterial therapy in atopic eczema. *Expert Opin Pharmacother*. 2010;11:929-936.
6. Moss T, Howes D, Williams FM. Percutaneous penetration and dermal metabolism of triclosan (2,4, 4'-trichloro-2'-hydroxydiphenyl ether). *Food Chem Toxicol*. 2000;38:361-370.
7. Allmyr M, Adolffson-Erici M, McLachlan MS, et al. Triclosan in plasma and milk from Swedish nursing mothers and their exposure via personal care products [published online ahead of print September 26, 2006]. *Sci Total Environ*. 2006;372:87-93.

8. Storer E, Koh KJ, Warren L. Severe contact dermatitis as a result of an antiseptic bath oil. *Australas J Dermatol*. 2004;45:73-75.
9. Wong CS, Beck MH. Allergic contact dermatitis from triclosan in antibacterial handwashes. *Contact Dermatitis*. 2001;45:307.
10. Jee R, Nel L, Gnanakumaran G, et al. Four cases of anaphylaxis to chlorhexidine impregnated central venous catheters: a case cluster or the tip of the iceberg? *Br J Anaesth*. 2009;103:614-615.
11. Nagendran V, Wicking J, Ekbote A, et al. IgE-mediated chlorhexidine allergy: a new occupational hazard [published online ahead of print March 26, 2009]? *Occup Med (Lond)*. 2009;59:270-272.
12. Garvey LH, Krøigaard M, Poulsen LK, et al. IgE-mediated allergy to chlorhexidine [published online ahead of print June 7, 2007]. *J Allergy Clin Immunol*. 2007;120:409-415.
13. Hanifin JM, Rajka G. Diagnostic features of atopic eczema. *Acta Derm Venereol*. 1980;92(suppl):S44-S47.
14. Yentzer BA, Ade RA, Fountain JM, et al. Improvement in treatment adherence with a 3-day course of fluocinonide cream 0.1% for atopic dermatitis. *Cutis*. 2010;86:208-213.
15. Fujita WH, McCormick CL, Parneix-Spake A. An exploratory study to evaluate the efficacy of pimecrolimus cream 1% for the treatment of pityriasis alba. *Int J Dermatol*. 2007;46:700-705.
16. Atopic dermatitis. American Academy of Dermatology Website. <http://www.aad.org/skin-conditions/dermatology-a-to-z/atopic-dermatitis>. Accessed April 12, 2012.
17. Zeppa L, Bellini V, Lisi P. Atopic dermatitis in adults. *Dermatitis*. 2011;22:40-46.
18. Carroll CL, Feldman SR, Camacho FT, et al. Adherence to topical therapy decreases during the course of an 8-week psoriasis clinical trial: commonly used methods of measuring adherence to topical therapy overestimate actual use. *J Am Acad Dermatol*. 2004;51:212-216.
19. Feldman SR, Camacho FT, Krejci-Manwaring J, et al. Adherence to topical therapy increases around the time of office visits [published online ahead of print May 10, 2007]. *J Am Acad Dermatol*. 2007;57:81-83.