

A double-blind study of tolerance and efficacy of a new urea-containing moisturizer in patients with atopic dermatitis

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Summary

Background Atopic dermatitis patients almost all use moisturizers to prevent and treat their skin disease. However, the safety and efficacy of moisturizers are rarely studied in this patient population.

Aims To evaluate the efficacy and tolerability of urea-containing moisturizers in subjects with atopic dermatitis.

Methods One hundred subjects with atopic dermatitis were randomized to apply either a new 5% urea moisturizer or a commercially available 10% urea lotion twice a day for 42 days. Scoring Atopic Dermatitis severity index (SCORAD) was performed at Day 0 and Day 42. Cosmetic acceptability questionnaires, adverse events, and a 5-point tolerance evaluation were administered or performed at Day 42.

Results Both study products were very well tolerated by subjects and only three subjects discontinued their participation in the study due to adverse events. Mean SCORAD significantly decreased between Day 0 and Day 42 by 19.76% and 19.23%, respectively, for subjects treated with the new 5% urea moisturizer or the 10% urea lotion ($P < 0.001$). There was no difference between the two products in SCORAD reduction; however, significantly more subjects preferred using the new 5% urea moisturizer as compared with the 10% urea lotion.

Conclusions Both the new 5% urea moisturizer and the 10% urea lotion improved atopic dermatitis and were very well tolerated. However, the cosmetic acceptability questionnaire showed that subjects preferred using the new 5% urea moisturizer over the 10% urea lotion.

Keywords: atopic dermatitis, moisturizer, efficacy, safety

Introduction

Atopic dermatitis is one of the most frequent skin diseases. It is characterized by the presence of pruritus, xerosis, and dry and erythematous plaques.^{1,2} The disease is often worst during winter months when the

weather is colder and drier. Treatments available for mild-to-moderate atopic dermatitis include moisturizers, topical corticosteroids, and topical immunomodulators. Topical corticosteroids are the most widely used topical treatments for atopic dermatitis.³ The use of moderate or potent corticosteroids in atopic dermatitis can be problematic as their chronic use can lead to skin atrophy. In the past few years, two topical immunomodulators have been approved for the treatment of atopic dermatitis: pimecrolimus and tacrolimus.⁴ They are usually used when low potency topical corticosteroids and

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moisturizers are not sufficient to control the disease. All patients must use a moisturizer to prevent and treat the disease.⁵ Mild cases of atopic dermatitis are often controlled with a moisturizer alone, which prevents potential side effects of topical medications.^{1,2,4}

Urea-containing moisturizers have been used successfully in patients with atopic dermatitis.^{6,7} They can improve xerosis associated with atopic dermatitis and prevent transepidermal water loss.⁸

The objective of this trial was to compare the tolerability and efficacy of a new 5% urea moisturizer to a 10% urea lotion in subjects with active atopic dermatitis.

Materials and methods

Study design

This was a two centers, randomized, double-blind study in subjects with atopic dermatitis. The study was conducted in accordance with the Declaration of Helsinki and International Conference on Harmonization and Good Clinical Practice Guidelines and was reviewed and approved by an institutional review board.

Subjects were randomized (1:1) to receive either the 5% urea moisturizer (Iso-Urea, La Roche-Posay Laboratoire Pharmaceutique, Asnières Cedex, France) or a 10% urea lotion. The study products were applied twice a day, in the morning and evening, on trunk and limbs. The study consisted of a screening visit, a randomization visit followed by two phone calls at Day 3 and Day 21 to verify compliance and tolerability, and a follow-up visit at Day 42 where efficacy and safety were evaluated.

The primary objective was to evaluate if the new 5% urea moisturizer applied topically during 6 weeks can improve atopic dermatitis as measured by the Scoring Atopic Dermatitis severity index (SCORAD). Secondary objectives were to study the tolerability of this 5% urea moisturizer in subjects with atopic dermatitis and to compare the efficacy of this new 5% urea moisturizer to the 10% urea lotion in improving atopic dermatitis.

Efficacy of the new 5% urea moisturizer was assessed with SCORAD. This validated tool evaluated atopic dermatitis severity by using a combination of signs (erythema, edema, crusts, lichenification, and excoriations), symptoms (pruritus and sleep loss), and extent of disease.⁹

Safety was assessed using a 5-point tolerance scale (1 = Very Good, 2 = Good, 3 = Average, 4 = Poor, 5 = Very Poor) and by evaluation of adverse events.

Study subjects

One hundred male or female subjects, age 18 years or older, diagnosed with atopic dermatitis with a SCORAD of 30 or less at screening and Day 0 were recruited at two centers. The main exclusion criteria were as follows: pregnancy and lactation, known allergy to one of the components of the study products, and any other dermatological conditions that could interfere with study evaluations. Subjects using topical corticosteroids for their atopic dermatitis were eligible as long as the dose and frequency of application was kept constant for at least 2 weeks before Day 0 and throughout the entire study. The washout period was 2 weeks for topical immunomodulators, 2 weeks for phototherapy, and 4 weeks for systemic treatment including PUVA therapy.

Study products

The 5% urea moisturizer was composed of the following ingredients: aqua/water, butyrospermum parkii/shear butter, glycerin, cyclohexasiloxane, urea, paraffinum liquidum/mineral oil, sodium lactate, cetearyl alcohol, PEG-100 stearate, glyceryl stearate, propylene glycol, glycine, tocopherol, stearic acid, myristic acid, palmitic acid, bisabolol, triethanolamine, dimethicone, dimethiconol, disodium EDTA, hydroxyethylpiperazine ethane sulfonic acid, xanthan gum, acrylates/C10-30 alkyl acrylate crosspolymer, citric acid, chlorhexidine digluconate, phenoxyethanol, methylparaben, propylparaben, fragrance.

The 10% urea lotion was composed of the following ingredients: aqua, urea, sodium lactate, paraffinum liquidum, octyldodecanol, caprylic/capric triglyceride, isopropyl palmitate, glycerin, PEG-7 hydrogenated castor oil, benzyl alcohol, methoxy PEG-22/dodecyl glycol copolymer, PEG-45/dodecyl glycol copolymer, dimethicone, magnesium sulfate, lactic acid, ozokerite, PEG-2 hydrogenated castor oil, sorbitan isostearate, hydrogenated castor oil.

Statistical analysis

This study had 80% power to detect a significant difference in SCORAD between Day 0 and Day 42 of at least 1.6 with a significance level of 5% assuming that baseline SCORAD scores were between 7 and 30 with a standard deviation of 3.8.

Analysis of variance (ANOVA) for repeated measures was used to analyze SCORAD data. As there were only two visits (Day 0 and Day 42) the efficacy evaluations

were performed on patients who completed both visits. For cosmetic acceptability and quality of life questionnaires, each answer was given a value of 0–3 (0 = Totally agree, 1 = Agree, 2 = Disagree, 3 = Totally disagree) and the answer “no comments” was considered a missing value. Missing values were replaced with the mean of all answers if at least 50% of the questions were answered by the patients. Patients who answered >50% of the questions with “no comments” were excluded from the analysis. These values were added for each patient from each group and for each questionnaire. The mean was calculated for each group and compared with a Student's *t* test. The mean tolerance was compared using a Student's *t* test to analyze the differences between the two study products. All analyses were performed with a significance level of 0.05.

Results

Subjects

Between March 2007 and October 2007, a total of 100 subjects (29 males and 71 females) between 18 and 70 years of age were randomized. Mean age was 37.5 and 34.7 for subjects randomized to the new 5% urea moisturizer and the 10% urea lotion, respectively. There were 14 males and 36 females in the new 5% urea moisturizer group and 15 males and 35 females in the 10% urea lotion group. Eighty-eight subjects completed the study (Day 42). Three subjects had an early termination visit because of adverse events and nine subjects were lost to follow up (Fig. 1). All subjects that had an early termination visit were included in the efficacy evaluation analysis. Four subjects were excluded from the SCORAD analysis, the cosmetic acceptability and the quality of life questionnaire; three for noncompliance to the protocol as they missed >30% of applications and one subject who applied the study product until Day 42 but was only able to come to the clinic on Day 77 because of an adverse event (enteritis).

Efficacy

Mean SCORAD values at Day 0 and Day 42 are shown in Figure 2. There was a statistically significant decrease in mean SCORAD at Day 42 compared with baseline for subjects treated with the new 5% urea moisturizer (19.76% reduction; range from 15.83 to 20.35) and with the 10% urea lotion (19.23% reduction; range from 17.01 to 21.40) ($P < 0.001$). The

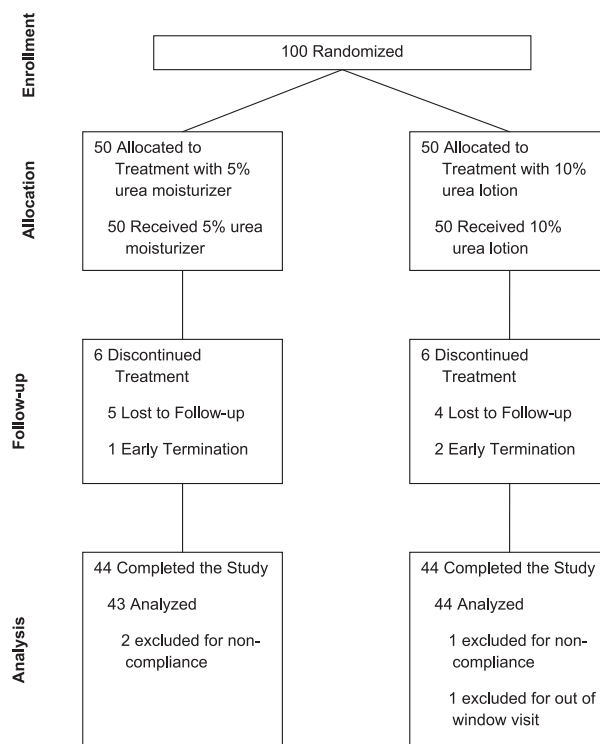


Figure 1 Subject disposition.

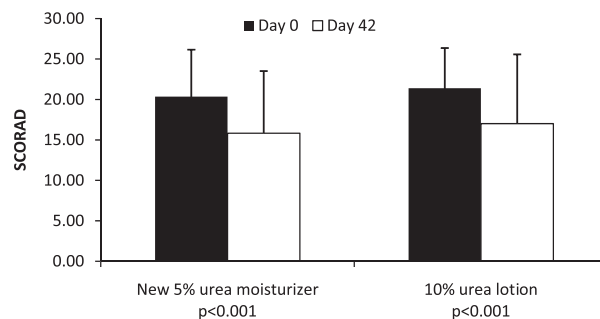


Figure 2 Mean SCORAD over time in both groups of subjects. Decrease was statistically significant at Day 42 when compared with baseline ($P < 0.001$).

difference in SCORAD between subjects treated with the two study products was not statistically significant ($P = 0.362$).

Safety

Both study products were well tolerated by most subjects. There was no serious adverse event in this trial. Twenty-two of the 100 subjects included in this study presented at least one adverse event during the study. A maximum of two adverse events per subject

was observed. Only five adverse events were possibly or probably related to the study products with three of them of mild intensity and all of them related to the skin. Three patients withdrew from the study because of adverse events. One subject randomized to the 10% urea lotion withdrew because of irritant contact dermatitis. Another subject randomized to the new 5% urea moisturizer withdrew because she had erythema on her eczema plaques and a third subject randomized to the 10% urea lotion withdrew because of pruritus. The remaining 21 adverse events were not related to the study products and were minor medical problems such as common cold and headache that are expected during a 42-day period.

Overall tolerance was evaluated using a 5-point scale at Day 42. All subjects who had a Day 42 visit were included in the tolerance evaluation. Mean values at Day 42 are shown in Figure 3. Both study products were well tolerated and the difference in tolerance between subjects treated with the new 5% urea moisturizer or treated with the 10% urea lotion was not significant ($P = 0.446$).

The cosmetic acceptability and the quality of life were evaluated using two questionnaires that were filled by subjects at Day 42. An English translation of these two French questionnaires is provided in Tables 1 and 2. Subjects who did not complete the Day 42 visit or who had compliance <70% were excluded from the questionnaire analyses. Mean scores are shown in Figures 4 and 5. Cosmetic acceptability was significantly better (lower score) for subjects treated with the new 5% urea moisturizer as compared with subjects treated with the 10% urea lotion ($P = 0.001$). There was a trend toward a higher beneficial impact on the quality of life for the new 5% urea moisturizer as compared with the 10% urea lotion ($P = 0.079$).

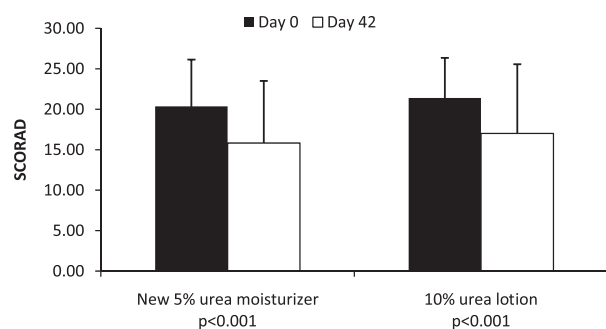


Figure 3 Mean tolerance values at Day 42 for subjects treated with the new 5% urea moisturizer or with the 10% urea lotion ($P = 0.446$).

Table 1 Cosmetic acceptability questionnaire

The product...	
A	Has a pleasant texture
B	Texture has just the right thickness
C	Texture has just the right fluidity
D	Has a pleasant scent
E	Has an appealing look
F	Can be applied easily
G	Penetrates rapidly
H	Does not leave the skin shiny
I	Does not leave the skin too oily or not oily enough
J	Does not leave the skin tacky shortly after the application
K	Allows one to dress rapidly after application
L	Does not lead to a feeling of discomfort at the time of application
M	Leaves the skin soft
N	Leaves the skin supple
O	Leaves the skin with a comfortable feeling all day
P	Moisturizes immediately upon application
Q	Moisturizes skin all day
R	Relieves feeling of discomfort immediately upon application
S	Relieves feeling of discomfort all day
T	Is convenient to use
U	Is generally pleasant

Table 2 Quality of life questionnaire

My skin...	
A	Has fewer itching attacks
B	Hurts less
C	Burns less
D	Is less tight
E	Does not bother me
F	Is less rough
G	Is less red
H	Is less dry
I...I	Am sleeping better
J	Wake up less at night because of itching
K	Wake up more rested
L	Am less anxious
M	Am less worried
N	Am more cheerful
O	Am more sociable
P	Find it easier to express my self
Q	Feel better
R	Feel more like others
S	Like the texture of the cream
T	Like my skin better
U	Am less embarrassed performing daily activities
V	Feel generally calmer

Discussion

This study suggests that both the new 5% urea moisturizer and the 10% urea lotion applied topically twice a day during 6 weeks can improve mild to

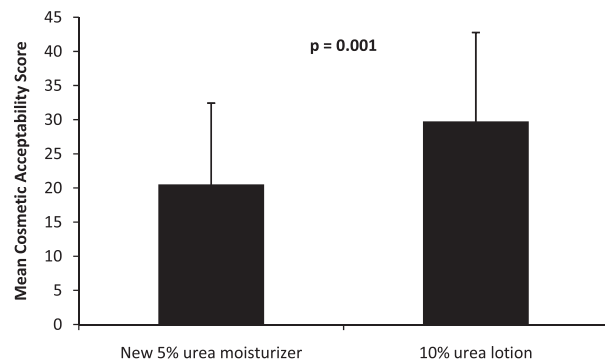


Figure 4 Mean score for the cosmetic acceptability questionnaire for subjects treated with the new 5% urea moisturizer or with the 10% urea lotion.

moderate atopic dermatitis as measured by SCORAD. The exact mechanism of action of urea-containing moisturizers in atopic dermatitis has not been well studied. The improvement in dermatitis may be linked to its known effect on skin hydration which may in turn improve skin barrier properties and decrease antigen and irritant penetration into the skin.

Subjects from both groups presented similar SCORAD value at time of randomization which was suggestive of mild to moderate atopic dermatitis. Despite a higher urea concentration in the 10% urea lotion there was no difference in efficacy, as measured by SCORAD reduction between the two products. It is important to note that in addition to urea concentrations the two emollients had different formulations and textures. Therefore, this study did not compare two concentrations of urea but two completely different products.

Both study products were well tolerated by subjects with mean tolerability scores between very good and good. Despite a higher urea concentration in the 10%

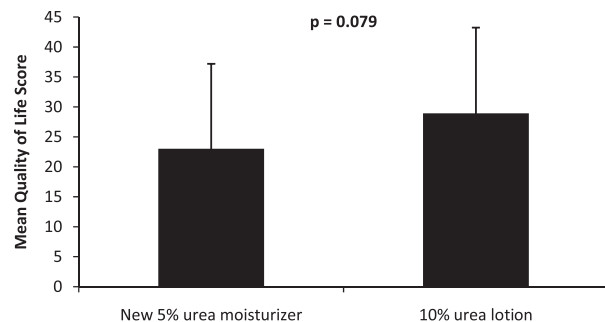


Figure 5 Mean score for the quality of life questionnaire for subjects treated with the new 5% urea moisturizer or with the 10% urea lotion.

urea lotion there was no difference in tolerability between the two products. As only subjects with mild to moderate atopic dermatitis were recruited in this study, the tolerability in severe patients is unknown. This study allowed the use of a stable dose of topical corticosteroids, the tolerability of the two urea products when used in monotherapy in atopic dermatitis has not been studied. However, most patients with active atopic dermatitis are treated with topical corticosteroids, therefore results of this study are more representative of real life dermatology practice than a study using only a urea moisturizer in monotherapy. The results obtained in this study have to be confirmed in children with atopic dermatitis and in patients with severe atopic dermatitis.

Evaluation of cosmetic acceptability showed that subjects significantly preferred the new 5% urea moisturizer over the 10% urea lotion. This could be related in part to the fact that the 5% urea moisturizer is an oil-in-water emulsion as opposed to the 10% urea lotion which is a water-in-oil emulsion. There was also a tendency toward a higher beneficial effect of the new 5% urea moisturizer on improving quality of life as compared with the 10% urea lotion. This tendency was observed despite the absence of difference in efficacy and tolerability. It is possible that this tendency is related to the cosmetic acceptability of the new 5% urea moisturizer. The success of topical treatments depends not only on the ability of the product to control the disease but also on patient compliance linked to the cosmetic qualities of the product.

In conclusion, this study suggests that both the new 5% urea moisturizer and the 10% urea lotion can improve atopic dermatitis. Both formulations were also very well tolerated. There was no statistically significant difference between the new 5% urea moisturizer and the 10% urea lotion in either efficacy or tolerability. However, patients preferred using the new 5% urea moisturizer as shown by the lower cosmetic acceptability score of the 10% urea lotion.

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