Efficacy and Tolerance of a Topical Skin Care Regimen as an Adjunct to Treatment of Facial Rosacea

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Retinaldehyde, a member of the retinoid family, may be beneficial when combined with the anti-inflammatory properties of dextran sulfate, along with hesperidin methyl chalcone, which reinforces vessel walls. The purpose of this study was to assess the usefulness and tolerability of a topical skin care regimen as an adjunct to treatment of facial rosacea when using a cream containing retinaldehyde 0.05%, dextran sulfate 0.3%, and hesperidin methyl chalcone 0.2% during a 6-month period in patients suffering from facial rosacea.

Rosacea is a chronic, cutaneous disorder characterized by a remitting, relapsing clinical course that may lead to significant facial disfigurement. Rosacea occurs most commonly in individuals aged 30 to 50 years and develops gradually in 4 stages: (1) facial flushing associated with stress, sun exposure, menstrual cycles, alcohol consumption, temperature changes, or spicy foods; (2) erythema, edema, or both, and ocular symptoms; (3) inflammatory papules and pustules; and (4) rhinophyma.[1] Many etiological factors have been considered, such as vascular regulation disorders and *Demodex* mite infestation. In stage 4 there is continued, increased skin and ocular inflammation.

Topical retinoids may be used as an adjunct to treatment of rosacea. Indeed, retinoic acid has beneficial effects on the vascular component of rosacea.[2] The drawbacks of treatment with retinoic acid include delayed onset of effectiveness, as well as the development of adverse effects (eg, skin dryness, erythema, burning, and stinging) early on in treatment that may temporarily aggravate lesions and lead to treatment nonadherence. Retinaldehyde is an intermediate compound in the natural metabolism of retinoids[3] and is the direct precursor of retinoic acid. The epidermal keratinocytes with a pertinent stage of differentiation are capable of oxidizing retinaldehyde to generate the active retinoic acid ligand. A higher tolerance in photodamaged skin was shown with retinaldehyde versus retinoic acid, with similar efficacy.[4,5] A higher tolerance of retinaldehyde makes it more suited for sensitive, irritated

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TABLE 1
Distribution of Fitzpatrick Skin Types

Fitzpatrick Skin Type	Patients, %
I	43
II	9
III	42
IV	6

skin in conditions such as rosacea and red face syndrome.[6] A study by Vienne et al[7] demonstrated that daily application of retinaldehyde 0.05% cream for 5 months yielded positive, statistically significant outcomes in 75% of patients. Specifically, improvements were found in erythema and telangiectasias, which are the vascular components of rosacea. In vitro studies have demonstrated that retinaldehyde inhibits vascular endothelial growth factor expression, which occurs via the anti–AP1 transcription factor activity.[8,9] However, dextran sulfate is a polysulfated carbohydrate with anti-inflammatory properties,[10] and hesperidin methyl chalcone reinforces the vein walls.

Our study assessed the efficacy and tolerance of a topical skin care regimen that was used during a 6-month period, combining retinaldehyde 0.05%, dextran sulfate 0.3%, and hesperidin methyl chalcone 0.2% as an adjunct to treatment of facial rosacea.

MATERIALS AND METHODS

Patients

Ninety-six patients with stage 1, 2, or 3 rosacea were included in this open-label, multicenter study conducted in Estonia and Latvia from November 2005 to July 2006. Patients applied a cream to the face once daily that contained retinaldehyde 0.05%, dextran sulphate 0.3%, and hesperidin methyl chalcone 0.2% either in the morning or in the evening for 6 months. To protect the skin from sun exposure, patients applied a broad-spectrum sunscreen with an SPF of 50 or higher that contained a combination of titanium dioxide, zinc oxide, and tocopherol precursor.

Clinical Efficacy

Clinical signs were evaluated during the 6-month period at 4 visits, with the first visit at baseline, and on days 60, 120, and 180. A 4-point scale was used to evaluate the clinical signs where 0=absent, 1=slight, 2=moderate, and 3=severe. Objective criteria, including erythema, telangiectasia, skin dryness, and scaling were evaluated by investigators. Subjective criteria, including pruritus, skin discomfort, burning sensation, skin tightness, and facial flushing were evaluated by the patients. Digital photographs of the patients were taken during each of the 4 visits.

Global efficacy was evaluated at days 60, 120, and 180 using a 5-point scale where 0=none, 1=slight, 2=moderate, 3=notable, and 4=very notable.

Global tolerance was evaluated at the time of application using a 4-point scale where 0=very bad, 1=bad, 2=good, and 3=very good. Patient and investigator satisfaction was also evaluated.

Statistical Analysis

All statistical tests were 2-sided. The risk of type I error (α) was set at 5%. Student *t* test or Wilcoxon signed rank test and Shapiro-Wilk normality tests were performed to check the efficacy parameters, including objective and subjective criteria, number of facial flushes, and overall efficacy, as well as the global tolerance of the treatment.

RESULTS

Patients

The average age of the patients was 44 years and the majority of patients (93%) were women. Table 1 shows the distribution of the patients' Fitzpatrick skin types, and Table 2 shows the distribution of patients with normal, combination, and oily skin types.

TABLE 2
Distribution of Skin Types

Skin Type	Patients, %
Normal	16
Oily	41
Combination	43

TABLE 3
Factors Inducing Facial Flushes

Factors	Patients, %
Temperature variation	88
Alcohol consumption	87
Sun exposure	69
Spicy foods	56
Cosmetics	39

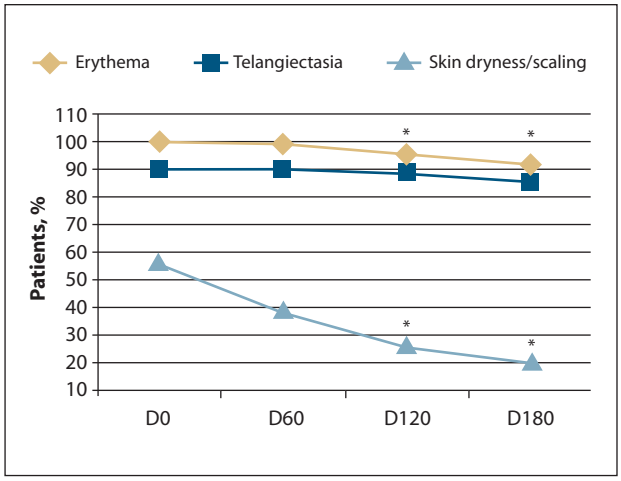

Figure 1. Evolution of objective clinical criteria with significant improvement throughout the treatment period of 180 days. Clinical criteria were evaluated by dermatologists. Asterisk indicates $P<.0001$ versus baseline.

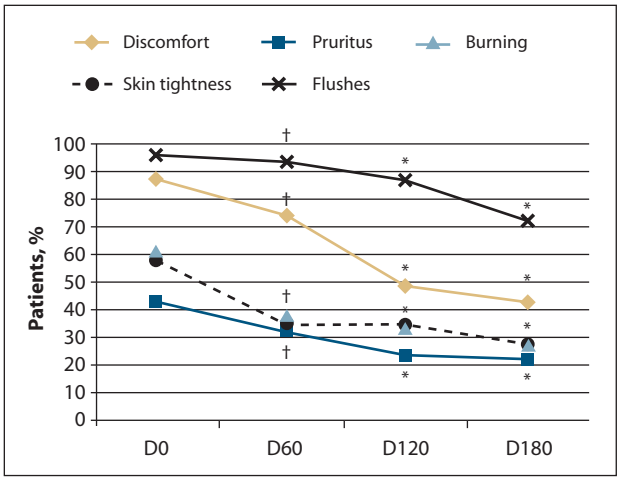

Figure 2. Evolution of subjective clinical criteria with significant improvement at day 60 and continued improvement through day 180. Subjective criteria were evaluated by patients. Asterisk indicates $P<.0001$ versus baseline; dagger, $P<.0005$ versus baseline.

A family history of rosacea spanning nearly 11 years was reported in 54% of the patients. Patients presented an average of 3 facial flushes per day and 17 facial flushes per week. The mean duration of facial flushes was 11 minutes.

The patients reported 1 or more factors inducing facial flushes (Table 3). Rosacea affected the patients' quality of life by disrupting their activities and relationships. Fifty-five percent reported a disruption of professional activities; 49% reported a disruption of leisure activities (eg, sports); and 49% reported a disruption of social relationships.

Within 6 months of the study, 30% of the patients received one or more therapeutic or cosmetic treatments for rosacea. Twenty percent of patients had used topical skin care products; 13% of patients had used topical antibiotics; 8% of patients had used systemic antibiotics; and 3% of patients had used azelaic acid or resorcin solution.

Clinical Efficacy

All the clinical criteria were significantly improved ($P<.0001$) through the 6-month treatment period (Figure 1). All subjective criteria were significantly improved ($P<.0005$) at day 60. Improvement continued through day 180 ($P<.0001$) (Figure 2).

Decreased frequency and duration of facial flushes through day 120 was a primary efficacy parameter. The number of facial flushes per day and per week and the duration of facial flushes statistically decreased ($P<.0001$) in a highly significant way from day 60 and continued decreasing from day 60 to day 120 in a statistically significant way ($P<.0001$), as well as from day 120 to day 180 ($P<.0001$) for the 3 efficacy parameters.

At day 180, the investigators reported global efficacy as notable or very notable in 46% of the patients. This improvement was visible in the digital photographs taken at each of the 4 visits.

Tolerance and Adherence

The investigator reported global tolerance as good or very good in 93%, 94%, and 96% of the patients at days 60, 120, and 180, respectively. Adherence ranged from 96% at day 60 to 86% through day 180.

Patient and Investigator Satisfaction

At day 60, 90% of the investigators and 88% of the patients reported the usefulness of the cream containing retinaldehyde 0.05%, dextran sulfate 0.3%, and hesperidin methyl chalcone 0.2% as an adjunct to treatment of facial rosacea as satisfactory or very satisfactory.

At day 180, 71% of the investigators reported that the cream containing retinaldehyde 0.05%, dextran sulfate 0.3%, and hesperidin methyl chalcone 0.2% was more effective than the usual products, and 95% of the patients wanted to continue the treatment.

DISCUSSION

Great strides have been made during the last decade in treating rosacea. For mild pustular and papular rosacea, topical prescription agents such as metronidazole and azelaic acid have been introduced. For the more severe forms of pustular and nodular rosacea, oral tetracycline antibiotics have been introduced. In some cases, isotretinoin has been used. One of the most challenging aspects of rosacea is the facial erythema that may appear to be the only symptom, or may accompany other manifestations, and for which most traditional treatments fail or are only minimally effective. Most patients have relied on expensive intense pulsed light devices or pulsed dye

lasers for treatment. In our study, we demonstrated the effectiveness of a topical skin care regimen that was used during a 6-month period, which contained a cream that combined retinaldehyde 0.05%, dextran sulfate 0.3%, and hesperidin methyl chalcone 0.2% as an adjunct to treatment of facial rosacea.

Rosacea appears most often in women with fair skin.[11] Feldman et al[12] noticed that among 1.1 million outpatient visits for rosacea in the United States, 96% were white individuals.

Treatment of rosacea includes multifaceted management.[13] For mild rosacea, patients are instructed to avoid sun exposure, alcohol consumption, hot drinks, spicy foods, and stimulants such as caffeine. For rosacea in later stages, drug treatment is often necessary. In our study, the retinaldehyde 0.05%, dextran sulphate 0.3%, and hesperidin methyl chalcone 0.2% cream was used with and without the combination of other topical or systemic treatments. We have shown that all clinical objective criteria (erythema, telangiectasia, skin dryness, and scaling) and subjective criteria (pruritus, skin discomfort, burning sensation, skin tightness, and facial flushes) were significantly improved.

The tested cream was highly tolerated when used under the usual conditions, either alone or associated with other treatments. Patients with rosacea have very sensitive skin and need nonirritating formulations of cleansers and other skin care products.[14] Because of barrier dysfunction or vascular hyperreactivity, patients must avoid cosmetic formulations leading to skin dryness and other irritation.[15,16] In our study, the high level of patient adherence over the 6-month treatment period demonstrated a high level of acceptability.

In conclusion, the retinaldehyde 0.05%, dextran sulphate 0.3%, and hesperidin methyl chalcone 0.2% cream is a useful adjunct to treatment of facial rosacea.

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