Pharmacology and therapeutics

Adapalene vs. metronidazole gel for the treatment of rosacea

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Abstract

Background Rosacea is a common, chronic dermatosis that requires long-term therapy. Oral isotretinoin and topical and/or oral antibiotics are effective, but their usage may be limited due to side-effects.

Objective The goal of the study was to compare the efficacy of topical adapalene gel (0.1%) and topical metronidazole gel (0.75%) in the treatment of patients with papulopustular rosacea.

Methods This study included 55 patients with papulopustular rosacea. Diagnostic efforts were focused on clinical and histological features. Patients were randomly assigned to the adapalene ($n = 30$) and metronidazole ($n = 25$) groups. Sunlight protection factor 20 cream was used to protect all patients from sunlight. The characteristics and numbers of inflammatory papules, pustules, erythema and telangiectasia were scored at baseline and after 2, 4, 8 and 12 weeks. Side-effects were recorded at each visit.

Results Fifty patients, 27 in the adapalene group and 25 in the metronidzaole group, completed the study. Significant reductions in the total number of inflammatory lesions were found in the adapalene group compared with the metronidazole group. There was no significant difference in the scores of erythema and telangiectasia in the adapalene group. However, a significant reduction in erythema was seen in the metronidazole group.

Conclusions Adapalene gel is well tolerated and can be used as an alternative for topical treatment of papulopustular rosacea.

Introduction

Rosacea is a common and well-recognized chronic cutaneous disorder primarily affecting the face, characterized by remissions and exacerbations. Diagnosis of rosacea is based on one or more of the primary features (flushing, nontransient erythema, papules, pustules and telangiectasia). Also, one or more of the secondary features (burning or stinging, plaques, dry appearance, edema, ocular manifestations, peripheral location and phymatous changes) may be included in the diagnosis.[1]

Rosacea affects females three times as often as males, and usually occurs between the ages of 30 and 50 years. Affected patients may give a history of acne vulgaris at a younger age and episodes of flushing. The diagnosis of rosacea depends on clinical and histopathological features.[1–3]

Systemic agents, such as tetracyclines, erythromycin, metronidazole and isotretinoin may be useful. However, the side-effects of these drugs limit the duration of treatment, leading to recurrences.[4,5] To enhance therapeutic efficacy with reduced side-effects, antibiotics (clindamycine and erythromycine), metronidazole and azelaic acid are used for topical treatment alone or in combination with systemic drugs. The effect of topical metronidazole in patients with rosacea has been established in a number of studies.[6–8] Topical tretinoin and isotretinoin cream have been tried. Side-effects, such as irritation, have been observed for these drugs.[9–11]

Adapalene is a new naphthoic acid derivative with potent retinoic acid receptor agonist activity and anti-inflammatory properties. Adapalene has been demonstrated to be safe and efficacious in topical treatment of acne and to have a low skin-irritation potential.[12]

The aim of this study was to compare the efficacy and safety of adapalene and metronidazole in the treatment of papulopustular rosacea.

Patients and Methods

The study was a randomized, investigator-blind comparison between adapalene gel (0.1%) and metronidazole gel (0.75%). A double-blind format was not used because the study drugs were not label-blinded commercial products contained in tubes of different sizes and shapes. Treatment protocols were different in each group.

Patients who had been diagnosed with papulopustular rosacea according to the criteria given by the Standards of the National Rosacea Society Expert Committee,[1] with at least 10 papules or pustules, were randomly included in the study. In order to minimize

Table 1 Patient characteristics

Patient characteristic	Adapalene	Metronidazole
Number of male/female patients	8/19	7/16
Mean age (years) (with range)	47.3 (23–75)	45.4 (25–67)
Mean disease duration (years) (with range)	6.1 (0.6–39)	4.3 (0.5–20)
Mean (SD) baseline number of papules	6.88 (1.57)	6.65 (1.30)
Mean (SD) baseline number of pustules	5.22 (0.97)	5.39 (1.07)
Mean (SD) baseline erythema grading	2.07 (0.67)	2.30 (0.76)
Mean (SD) baseline telangiectasia grading	1.48 (0.84)	1.47 (1.08)

the effects of preceding therapy, previous topical rosacea medications and systemic antibiotics were stopped at least 2 and 4 weeks prior to the study, respectively. Patients with underlying systemic and/or dermatologic disorders were excluded. Patients with marked ophthalmic complications, steroid rosacea, other diseases or medications that may interfere with adapalene and metronidazole (such as previous systemic or topical retinoic acid) usage were excluded. Pregnant or nursing patients were also excluded from the study. Written informed consent was obtained following an explanation of the purpose of the study and the risks concerning the teratogenic effects of adapalene.

Patients were randomly assigned to two groups to receive topical adapalene gel ($n = 30$) and topical metronidazole gel ($n = 25$). The adapalene group were treated with topical adapalene gel once daily in the evening, and the metronidazole group were treated topically twice a day for 12 weeks. All patients were also given sunlight protection factor (SPF) 20 cream (Sebamed Cream, Sebapharma GmbH, Boppard, Germany) to protect the skin against sunlight. Patients were evaluated at baseline and after 2, 4, 8, and 12 weeks of treatment. The same investigator carried out all evaluations at each visit.

General patient information, previous rosacea history and baseline severity scoring of illness were recorded. The therapeutic progress notes were assessed during each visit. The efficacy of the treatment was assessed by the number of inflammatory papules and pustules, and by the severity of erythema and telangiectasia. Erythema and telangiectasia were graded on a four-point scale.[13] For erythema, the following grades were used.

0 No erythema.

I Mild; slight erythema, either with restricted central involvement or generalized over the whole face.

II Moderate; pronounced erythema centrally restricted or generalized on the face.

III Severe; severe erythema over the whole face.

For telangiectasia, the following grades were used.

0 No telangiectasia.

I Mild; fine vessels less than 0.2 mm in diameter covering less than 10% of the face.

II Moderate; several fine vessels and/or a few large vessels more than 0.2 mm in diameter covering 10–30% of the face.

III Severe; many fine and/or large vessels covering more than 30% of the face.

Descriptive statistics were expressed as mean ± SD (standard deviation). The mean erythema and telangiectasia scores and the mean numbers of papules and pustules were compared between groups using the Mann–Whitney *U*-test. Changes in values over time were analysed using the Friedman test. When the Friedman test showed a significant difference, a Wilcoxon test was performed to determine the times at which the values changed. The level of significance was set at $P < 0.05$.

Results

Patient characteristics

There was no significant variation in baseline patient characteristics in terms of demographic data and disease activity (e.g. numbers of papules and pustules, and erythema and telangiectasia scores). Fifty-five patients suffering from papulopustular rosacea were enrolled in the study. The mean age of the patients was 46.5 years (range 23–75 years) and the mean disease duration was 5.2 years (range 0.5–39 years) (Table 1). In the adapalene group, three patients (two females and one male) were discharged from the study due to side-effects (erythema in two patients, and burning and skin irritation in one). In the metronidazole group, two female patients discontinued the study for unknown reasons.

Papules and pustules

Although both groups showed a significant decrease in the number of papules and pustules during the treatment period ($P < 0.05$), adapalene produced significantly greater reductions than metronidazole in the number of papules at the end of the 12th week. There was no significant difference in the number of pustules at the end of the 12th week. The adapalene group showed a decrease in the numbers of papules and pustules from 6.89 ± 1.57 and 5.22 ± 0.97 at baseline to 1.22 ± 0.97 and 0.78 ± 0.11 at the end of the 12th week, respectively ($P < 0.05$), while the metronidazole group showed values of 6.65 ± 1.30 and 5.39 ± 1.07 decreasing to 1.86 ± 0.81 and 0.86 ± 0.54, respectively (Figs 1 and 2).

Treatment with adapalene gradually reduced the numbers of papules and pustules over the 12 weeks. In contrast, metronidazole showed most of its effect in the first month of treatment. Between 8 and 12 weeks of treatment, there was

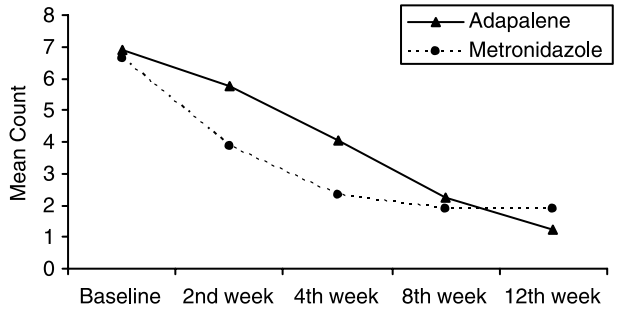

Figure 1 Changes in mean papule number during the 3-month treatment period

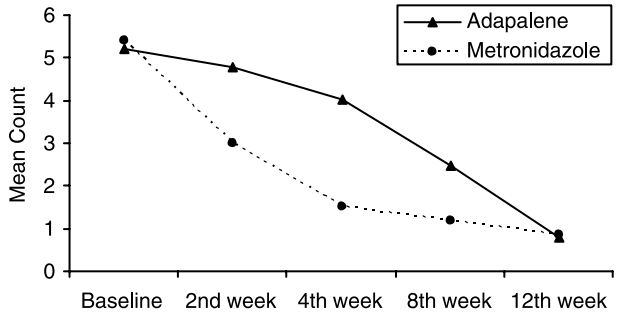

Figure 2 Changes in mean pustule number during the 3-month treatment period

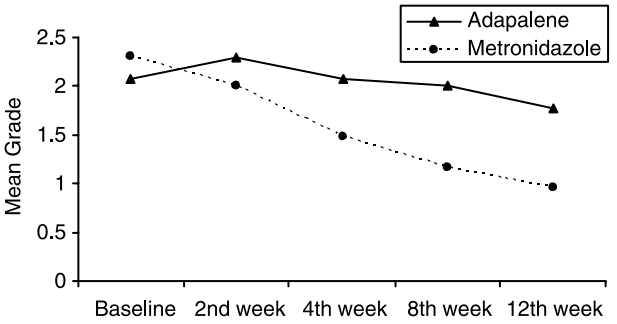

Figure 3 Changes in mean erythema grading during the 3-month treatment period

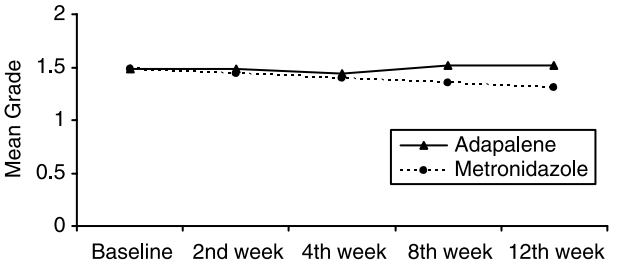

Figure 4 Changes in mean telangiectasia grading during the 3-month treatment period

no statistically significant change in the number of papules in the metronidazole group ($P > 0.05$).

Erythema and telangiectasia

During the first month of treatment, we did not observe any improvement in erythema in the adapalene group. During the second and third months, a minimal decrease in erythema was observed ($P > 0.05$). Also, there was no significant difference in telangiectasia ($P > 0.05$) in this group.

In the metronidazole group, the score for erythema decreased significantly with time ($P > 0.05$). However, there was no significant difference in the telangiectasia scores (Figs 3 and 4).

Adverse events

Metronidazole and adapalene were tolerated well, with acceptable side-effects. All of the patients tolerated the treatment for 3 months, except for three patients who stopped treatment because of a sensation of burning and skin irritation in the adapalene group, and two patients in metronidazole group.

During the first 2 weeks of treatment in both groups, varying degrees of sting and burning were experienced by the patients, which were tolerated more easily with time. An increase in facial erythema was observed during the first month of treatment in the adapalene group.

Discussion

Although the papules and pustules of rosacea can be treated with topical and/or systemic medications, the disease is characterized by remissions and exacerbations. Due to the chronic nature of the disease, there is a necessity for safe and effective long-lasting topical therapies.[14]

Topical metronidazole has been shown to be safe and effective in moderate to severe rosacea. It is highly effective for papules and pustules, but less effective in reducing erythema. The mechanism of action may be related to anti-inflammatory or immunosuppressive actions of the drug.[6]

Oral *cis*-retinoic acid (isotretinoin) has been shown to be dramatically effective in moderate to severe papulopustular-type rosacea.[3,4,10,15] However, topical retinoic acid derivatives are not included in the ordinary treatment of rosacea.

Ertl *et al.*[9] and Kligman[11] studied the efficacy of topical tretinoin for rosacea and found that topical tretinoin was effective in reducing the number of papules and pustules and the severity of erythema in patients with rosacea. Adapalene, a naphthoic acid derivative with potent retinoid properties, is a new drug proposed for the treatment of acne patients. It has anti-inflammatory and antiproliferative activity in *in vitro* and *in vivo* studies.[16] Adapalene was also less irritating then tretinoin gel when used in acne patients.[17] In our study, we found that adapalene gel (0.1%) had a strong effect on papules and pustules, but an insignificant effect on erythema and telangiectasia.

Pharmacologic and preclinical studies have demonstrated that adapalene has excellent follicular penetration and anti-inflammatory activity.[16] It has a high affinity for the retinoic acid receptors and its activity is similar to or greater than that of tretinoin. Like the other retinoic acids, adapalene may reduce photo-aging.[18,19] These effects may explain its mechanism of action on rosacea. Elastin degeneration, and inflammatory papules and pustules are histopathological and clinical events seen in rosacea. Elastin degeneration, which is usually due to actinic exposure, is probably a common cause of lymphatic failure which may lead to inflammatory lesions.[10]

The disadvantage of adapalene is its erythrogenic effect, although this irritant effect is less marked than that of the other retinoids. We found that most of the patients, even those with sensitive skin, became tolerant of this side-effect.

In our study, adapalene was significantly effective in decreasing the number of papules and pustules in patients with rosacea, but it was not effective in reducing erythema and telangiectasia within the 3-month treatment period.

The limitations of the study, in addition to the absence of a vehicle control, were that it was not double-blinded, that it studied only erythema, papules and pastules of rosacea, and that it lasted only 12 weeks. Multicenter, randomized, double-blinded studies continuing beyond 12 weeks are needed to further establish the effectiveness of adapalene in the management of rosacea.

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