Clinical trial

Investigator-masked comparison of tazarotene gel q.d. plus mometasone furoate cream q.d. vs. mometasone furoate cream b.i.d. in the treatment of plaque psoriasis

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Drug names
tazarotene: Tazorac
mometasone furoate: Elocon
betamethasone dipropionate: Diprosone
diflorasone diacetate: Maxiflor

Seventy-three patients with stable plaque psoriasis entered an investigator-masked trial comparing once-daily tazarotene 0.1% gel plus once-daily mometasone furoate 0.1% cream with twice-daily mometasone furoate 0.1% cream. The aim of the study was to determine whether tazarotene and mometasone furoate act synergistically — a previous study showed that tazarotene plus mometasone furoate offered greater efficacy than tazarotene alone, and this study investigated whether tazarotene plus mometasone furoate also offered greater efficacy than mometasone furoate alone.

The patients had psoriasis affecting up to 20% of their total body surface area, with at least moderate plaque elevation. Washout periods were: 2 weeks for UVB phototherapy or topical antipsoriatic therapies; 4 weeks for psoralen plus UVA (PUVA) therapy or systemic antipsoriatic drugs other than retinoids; and 8 weeks for oral retinoids. All patients gave written informed consent and the study was conducted in compliance with the ethical standards of the governing institutional review boards and the Declaration of Helsinki.

Patients were treated for up to 12 weeks. If they achieved clearance by week 4, or at least 50% global improvement by week 12, they were entered into the 12-week no-treatment follow-up phase.

Patients were evaluated every 4 weeks in terms of percentage global improvement, plaque elevation, scaling, erythema, and pruritus. They also rated the efficacy of their own treatment (as very effective, effective, neutral, ineffective, or less effective) and the duration of improvement in their psoriasis (as much better, better, somewhat better, indifferent, or worse than that achieved with other topical medications they had used in the past).

The two regimens were compared by analysis of variance, with the last recorded score for any patient who discontinued prematurely (due to lack of efficacy, adverse events, or disease flare) being carried forward to all subsequent visits.

Results

Patient demographics

A total of 73 patients (26 women, 47 men) were enrolled. Of these, 26 of 35 (74%) tazarotene/steroid-treated patients and 22 of 38 (58%) steroid-treated patients achieved $\geq 50\%$ global improvement in their psoriasis and entered the no-treatment phase. The patients' mean age was 44 years (range, 22–73 years) and 68% had suffered from psoriasis for more than 10 years.

Efficacy during treatment

The tazarotene plus steroid regimen achieved greater, and more rapid, global improvements in psoriasis, plaque elevation (Fig. 1), and scaling (Fig. 2) than the twice-daily steroid monotherapy regimen ($p \leq 0.05$ by week 4 or 8). Both treatment regimens achieved similar percentage reductions in erythema (49% and 43%, respectively) and pruritus (44% and 47%, respectively) during the treatment phase.

Efficacy post-treatment

The superiority of the tazarotene plus steroid treatment over steroid monotherapy was sustained throughout the 12-week post-treatment period, with significant differences between the two treatment groups at 4 weeks post-treatment for global improvement, plaque elevation, and scaling. Furthermore, although both treatment groups had achieved comparable reductions in erythema and pruritus during the treatment phase, between-group differences emerged during the post-treatment phase. In the tazarotene plus steroid group, almost all the improvements in

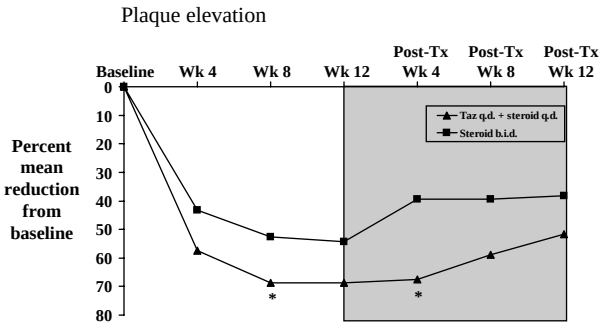

Figure 1 Mean percentage reduction in plaque elevation score. $*P \leq 0.05$ compared with steroid monotherapy

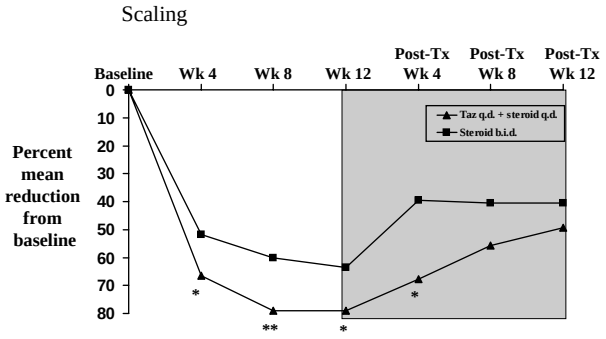

Figure 2 Mean percentage reduction in scaling score. $*P \leq 0.05$, $**P \leq 0.01$ compared with steroid monotherapy

erythema and pruritus were sustained during the 12-week post-treatment phase; however, in the steroid monotherapy group, the majority of the improvement in erythema and almost half the improvement in pruritus were lost within the first 4 weeks of the post-treatment phase.

Adverse effects

Only one adverse effect that was drug related (possibly, probably, or definitely) was reported in the steroid monotherapy group (one [3%] patient reported dermatitis at week 12). In the tazarotene plus steroid group, drug-related adverse effects were reported with an incidence of 29% at week 4, 17% at week 8, 0% at week 12, 0% at post-treatment week 4, 0% at post-treatment week 8, and 3% at post-treatment week 12. The most common adverse effects were burning (11% of patients), pruritus (11%), irritation (9%), eruption (6%), and exacerbation or new occurrence of psoriasis (6%).

Patient discontinuations

In the treatment phase, a higher proportion of patients discontinued due to drug-related reasons in the steroid monotherapy group (32%) than in the tazarotene plus steroid group (14%). Drug-related discontinuations were largely due to lack of efficacy (three [9%] patients using tazarotene plus steroid and 12 [32%] patients using steroid alone). Only two patients discontinued due to adverse effects — both in the tazarotene plus steroid group (6%).

The difference in the rate of discontinuations in the two treatment groups was further exacerbated within the first 4 weeks of the post-treatment phase. This was attributable to 15 of the 22 patients (68%) in the steroid monotherapy group who had entered the no-treatment phase discontinuing due to disease flare within the first 4 weeks of no-treatment follow-up. In contrast, only three of the 26 patients (12%) in the tazarotene plus steroid group discontinued due to disease flare during this period (Fig. 3).

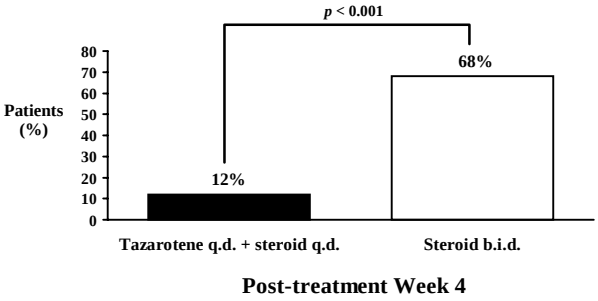

Figure 3 Percentage of patients entering the no-treatment phase who discontinued within the first 4 weeks of no treatment as a result of disease flare

Patient satisfaction

Patient ratings favored tazarotene plus steroid treatment over steroid monotherapy — at week 12, 79% vs. 43% of patients, respectively, rated their medication as "effective" or "very effective." After 12 weeks of follow-up, 83% vs. 60% of patients, respectively, rated their duration of clinical improvement as "better" or "much better" than previous medications.

Discussion

The results of this study complement those reported previously of a greater efficacy with tazarotene plus mometasone furoate than with tazarotene monotherapy.[1] Considering both studies together, it is now clear that a synergy exists when tazarotene is used in combination with mometasone furoate cream, with such a combination achieving more rapid clinical improvement and greater overall efficacy than either drug as monotherapy.

Furthermore, an additional advantage of combination tazarotene plus steroid therapy is that tazarotene can significantly reduce the degree of steroid-induced epidermal atrophy by promoting an increase in the thickness of the epidermis.[2]

A recent trial of tazarotene in combination with one of six corticosteroids has revealed that some steroids of similar potency are considerably more effective than others in enhancing the efficacy of tazarotene.[3] Of the steroids evaluated, the most efficacious when used adjunctively with tazarotene were betamethasone dipropionate 0.05% cream (a medium to high potency steroid), followed by mometasone furoate 0.1% ointment and diflorasone diacetate 0.05% ointment (both high potency steroids). Thus, the steroid potency is not necessarily a reliable indicator of its ability to enhance the efficacy of tazarotene treatment. Future clinical studies may yet find an even more powerful synergistic combination than the tazarotene plus mometasone furoate regimen in the study reported here.

Acknowledgment

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Clinical trial

Melasma treated with hydroquinone, tretinoin, and a fluorinated steroid

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A retrospective study was conducted in six Hispanic women, 35–55 years of age, with Fitzpatrick skin types IV to VI, presenting to an academic dermatology clinic for resistant melasma (Table 1). They had all been treated with topical hydroquinone (2–4%) without success prior to being seen in our clinic.

A Wood's lamp was used to determine whether the melasma was epidermal, dermal, or a combination of the two. The patients were treated with a mixture containing 0.05% tretinoin cream, 0.05% triamcinolone acetonide cream, 6% hydroquinone, and 0.1% ascorbic acid (as a preservative) applied at night, and a sun protection factor (SPF) 15 UVB-blocking sunscreen was applied each morning. They were instructed to use the mixture on the affected areas nightly for a period of 8 weeks. All of the patients were evaluated at baseline and monthly during the treatment period. Improvement in pigmentation was assessed at each subsequent visit by clinical examination and photography with polarized filters as well as black and white UV reflectance photography (Canfield Scientific, Inc.). Improvement was determined subjectively on a three-point scale as follows: I, mild improvement; II, moderate improvement; III, significant improvement.

Results

All six patients had a history of moderate melasma, which had been present for 6–20 years (mean, 10 years) as shown in Table 1. The majority were from Mexico and had previously used products containing 2–4% hydroquinone without much success. Table 2 lists the degree of improvement in all patients. Five of the six patients had at least moderate improvement. Figures 1–4 show the improvement in two of these patients.

Discussion

Melasma, one of the most common causes of acquired hypermelanosis, manifests as irregular brown macules which affect areas of the skin exposed to the sun, in particular the cheeks, forehead, nose, and chin. This disorder is most common in Hispanics, Blacks, and Asians, and predominantly affects women. Three clinical patterns of melasma have been described: centrofacial (most common), malar, and mandibular.[1,2] Melasma can also

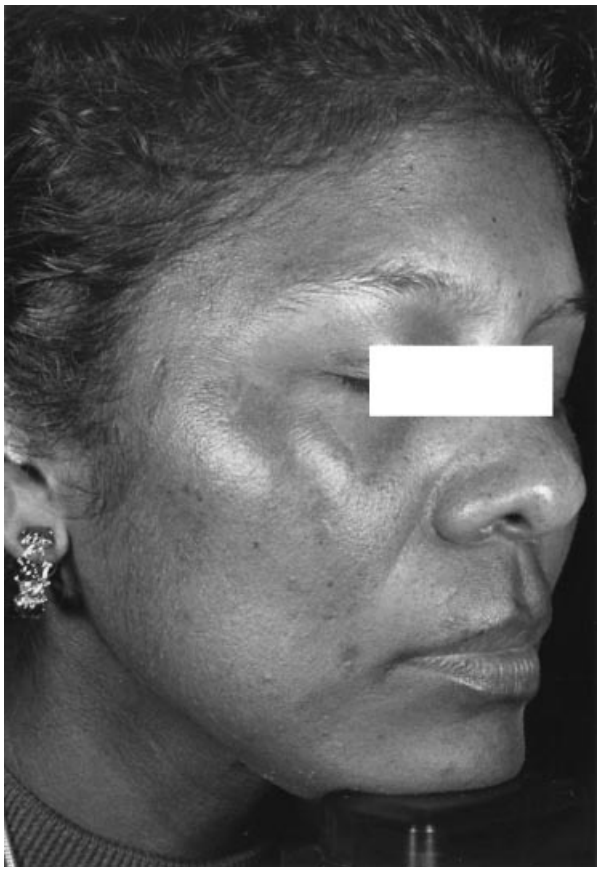

Figure 1 Patient 3 before treatment (UV photography)

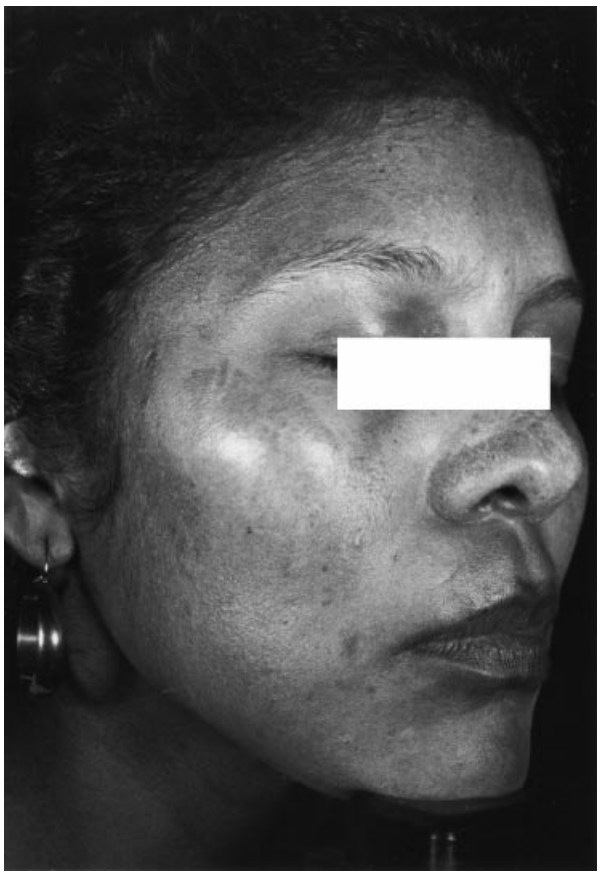

Figure 2 Patient 3 after 8 weeks of treatment (UV photography)

Table 1 Patient demographics

Patient	Age	Country of origin	Affected area	Duration of disease (years)	Severity	Type of melasma
1	39	El Salvador	Cheeks, upper lip	10	Moderate	Epidermal
2	37	Mexico	Cheeks	12	Moderate	Epidermal
3	35	Mexico	Cheeks	7	Moderate	Combination
4	35	Mexico	Cheeks	9	Moderate	Epidermal
5	55	Mexico	Cheeks, jaw	20	Moderate	Combination
6	32	Mexico	Cheeks, forehead	6	Moderate	Epidermal

Table 2 Results

Patient	Degree of improvement	Side-effects
1	I	Only used the formula twice weekly due to irritation of cheeks
2	II	Slight irritation and fine telangiectasias
3	III	No adverse effects
4	II	Slight irritation and fine telangiectasias
5	III	Slight irritation
6	III	No adverse effects

I, mild improvement; II, moderate improvement; III, significant improvement.

be divided into three types based on the appearance of the borders of macules under a Wood's lamp: epidermal, dermal, and mixed.

Although the precise cause of melasma is still unknown, several factors have been postulated in the pathogenesis of this condition, such as pregnancy, change in hormonal status, genetic influences, UV exposure, oral contraceptives, and thyroid dysfunction. The objective of therapy is to slow the proliferation and growth of melanocytes, inhibit the formation of melanosomes, and promote their degradation.

The treatment of melasma is often difficult, due to its recurrent nature and recalcitrance to treatment. While many patients respond to commercially available formulas containing 2–4% hydroquinone, combination creams are often used in those who do not respond to hydroquinone alone. Formulations demonstrating the most impressive results for resistant melasma contain hydroquinone in concentrations of 2% to 6%, together with tretinoin and topical steroids, such as Kligman's formula (0.1% tretinoin, 5% hydroquinone, and 0.1% dexamethasone).[3,4] Tretinoin helps to remove the stratum corneum, which enhances the penetration of hydroquinone. Tretinoin alone has also been shown to have depigmenting properties.[5–7] Topical steroids used in combination creams in previous studies have been of low potency; therefore, we elected to

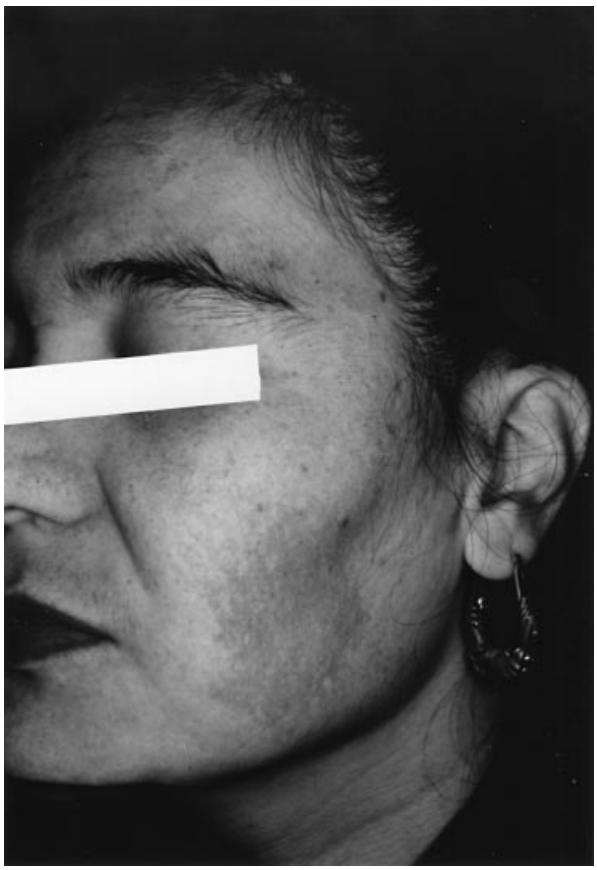

Figure 3 Patient 6 before treatment (using polarized filters)

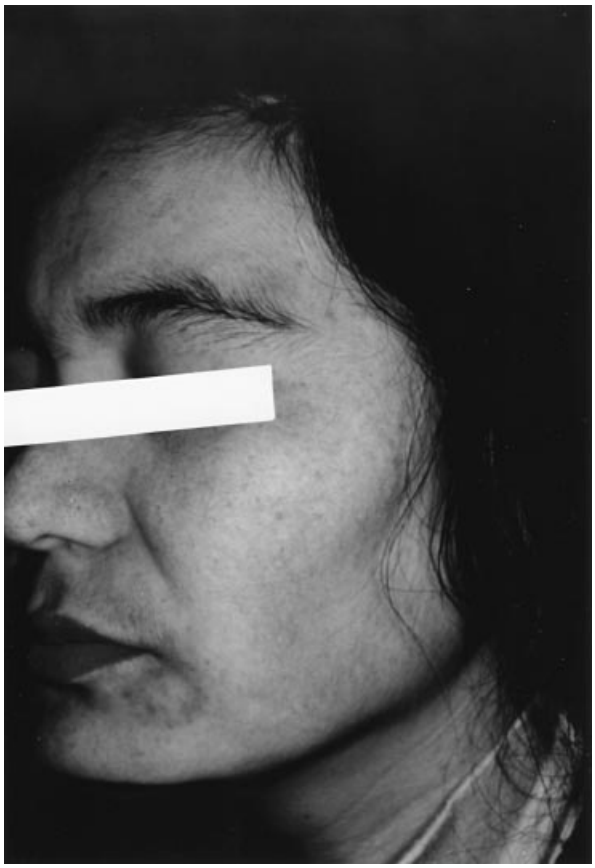

Figure 4 Patient 6 after 8 weeks of treatment (using polarized filters)

try a formula containing a stronger, fluorinated steroid to determine if more effective depigmentation could be achieved. Topical fluorinated steroids may produce beneficial effects, such as depigmentation and prevention of retinoid dermatitis, but can also lead to detrimental effects, such as cutaneous atrophy, telangiectasias, and steroid acne, all well-known steroid side-effects. We arbitrarily selected triamcinolone at a concentration of 0.05%, because lower potency steroids, both in our own unpublished observations, as well as in published reports, have not shown significant, rapid improvement in patients with resistant melasma.[8,9]

Our results showed moderate to significant improvement in five of six patients over an 8-week period. This improvement was more apparent when UV and polarized photography techniques were used, as demonstrated in Figs 1–4. Side-effects were mild and reversible upon discontinuation of the cream. Unfortunately, relapse is common in chronic melasma, and our five patients may require repeated use of this formula in the future.

One major drawback to our study is its small sample size and the uncontrolled, subjective method of evaluation. Recently described techniques in evaluating the degree of improvement in melasma, such as colorimetry and the melasma area and severity index (MASI), should be used in future trials with our formula. The improvement seen in the majority of our patients with resistant melasma warrants further study.

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