Cosmetic Color Improvement of the Nipple-Areola Complex by Optimal Use of Tretinoin and Hydroquinone

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BACKGROUND. **A successful treatment to improve the color of nipple-areola complex (NAC) has never been reported, although the number of women seeking the more attractively colored NAC is not small.**

OBJECTIVE. **To determine the effectiveness of our bleaching protocol for cosmetic improvement of the NAC.**

METHODS. **The protocol was composed of two phases: bleaching phase (4–8 weeks) and healing phase (4–6 weeks). 0.2–0.4% tretinoin aqueous gel was applied concomitantly with 5% hydroquinone, 7% lactic acid ointment for bleaching twice a day. Tretinoin was applied to the NAC with a small cotton applicator, while hydroquinone was widely applied beyond the NAC area. After obtaining sufficient improvement in NAC color, the application of tretinoin was discontinued and hydroquinone alone was continually applied in the healing phase until the reactive erythema was eliminated. Fifteen female patients were involved in this study.**

RESULTS. **The average treatment period was 16.6 weeks. Improvement of NAC color was obtained in 12 patients (80%) by the physician's estimation, and 11 patients (73%) satisfied with their final results. The treatment was repeated after a 1-month interval of tretinoin application in 4 patients: 2 desired further improvement in color, and 2 had the second course conducted to treat the postinflammatory hyperpigmentation on the surrounding mound induced by the first course.**

CONCLUSION. **This approach appeared to be most effective for cosmetic improvement of NAC color among treatments available so far.**

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THE NUMBER of females seeking a better-looking nipple-areola complex (NAC) is not small. Some patients complain about the size of nipple and/or areola, and others about the color of NAC; the number of the latter is apparently greater in Japan. In general, patients prefer lighter color to darker color. An NAC which looks bright pink is thought to be more attractive than a dark-brown one. Some patients have dark-looking NAC from childhood, but others develop them in adolescence or later. Up-regulations of female hormones after adolescence could affect the color of the NAC, and repeated mechanical stimulation such as rubbing by undergarments or sexual habits can cause postinflammatory hyperpigmentation of the NAC. Additionally, women of some races with dark skin often have dark NACs.

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No satisfactory method has ever been reported for treatment of NAC color, although there are several options: laser therapies, chemical peeling and tattooing. Lasers, such as Q-switch ruby laser, Q-switch Nd:YAG laser, and dye lasers, can change the color, but the results are often disappointing and can be miserable. Laser treatments for NACs sometimes lead to depigmentation and/or scarring, and it is hard to get a homogenous and natural appearance. Chemical peeling such as alpha-hydroxy acids or TCA combined with a bleacher such as hydroquinone is minimally effective in changing NAC color. Tattooing with white or pink color leads to unnatural appearance, recovery from which is almost impossible.

The authors previously described an aggressive and optimal use of tretinoin along with hydroquinone for various kinds of skin hyperpigmentation.[1,2] More than 8,000 patients with hyperpigmented skin lesions have been treated with the original method or its modifications in our facility over the past 7 years with successful overall results. In the present study, the modified protocol was applied to the patients who wanted improved NAC color, and the results were satisfactory.

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To our knowledge, this paper is the first one to demonstrate successful results on NAC color modification.

Patients and Methods

Preparation of Ointments

Tretinoin aqueous gels (tretinoin gel) at 2 different concentrations (0.2, and 0.4%) were originally prepared at the Department of Pharmacy, University of Tokyo, Graduate School of Medicine. The precise regimen of tretinoin aqueous gel was described before.[2] An ointment including 5% hydroquinone and 7% lactic acid (HQ-LA ointment), an ointment including 5% hydroquinone and 7% ascorbic acid (HQ-AA ointment), and an ointment including 5% kojic acid (KA ointment) were also prepared as well. Plastibase (petrolatum polyethylene ointment base, Taisho Pharmacology, Osaka, Japan) was used as the ointment base of the HQ-LA ointment, while the hydrophilic ointment was used for the HQ-AA and the KA ointments. Because tretinoin gel, HQ-LA, HQ-AA, and KA ointment (especially tretinoin gel) are pharmacologically unstable, fresh ointments were prepared at least once a month and stored in a dark and cool (4°C) place.

Evaluations of Results

Clinical evaluations (objective). Photographs were taken for every patient at baseline and after the treatment, and two experienced doctors (a dermatologist or cosmetic surgeon) who did not perform this treatment evaluated the clinical results via the photographs. The results were classified into 4 categories: "excellent" (improvement is apparent and the result is impressive), "good" (improvement can be recognized easily), "fair" (improvement can be recognized), and "poor" (improvement cannot be recognized via photos).

Patient satisfaction (subjective). Patients were interviewed about their level of satisfaction with the clinical results after the treatment. The patient was requested to estimate the clinical result and select one of three categories: "very satisfied," "slightly satisfied," and "not satisfied."

Patients

Each ointment was topically applied under signed informed consent in 19 Japanese women with complaints about their NAC color, and 15 of them who were followed up for more than 12 weeks were analyzed in this study. The other 4 patients could not be followed up for more than the 12 weeks minimum required, and some of them might have discontinued treatment because of irritation, although their reasons remain unclear. The age of patients varied from 18 to 42-year-old (age = 32.1 ± 4.2; mean ± SD).

Treatment Protocol

Our bleaching protocol is composed of two phases: a bleaching phase and a healing phase. In the bleaching phase, the pigmentation is aggressively treated, and transient adverse skin effects such as erythema and irritation are usually observed. Once satisfactory improvement is obtained, the healing phase is started in order to reduce the erythema and inflammation, taking care not to induce new postinflammatory hyperpigmentation.

Bleaching phase. Tretinoin gel and HQ-LA ointment were applied to the NAC twice a day. 0.2% tretinoin was used initially. Tretinoin gel was applied only on NAC areas using a small cotton-tip applicator, while HQ-LA ointment was applied beyond the NAC area (e.g., all over the whole breast mound). In cases in which severe irritant dermatitis was induced by HQ-LA ointment, HQ-AA or KA ointment was used instead. Patients were requested to visit our hospital at 1, 2, 4, 6 and 8 weeks after starting this treatment, and every 4 weeks afterward. When the appropriate skin reaction (that is, mild erythema and scaling) was not observed at 1 week, the concentration of tretinoin was changed to 0.4%. In most cases, it took 4–8 weeks to finish this phase. If the patients desire further improvement, a second treatment course with the same protocol can be started after 4–6 week's interval (= healing phase described below).

Healing phase. After sufficient improvement of NAC color was obtained, the application of tretinoin gel was discontinued, but that of HQ-LA ointment was continued. In cases in which erythema was not reduced at all after a few weeks' application of HQ-LA ointment, HQ-LA ointment was also discontinued and HQ-AA or KA ointment was applied until the redness was sufficiently reduced. It usually took 4–6 weeks to complete this phase. The total period of a single treatment course to finish both phases was usually 8–12 weeks. Topical corticosteroids were not employed in either the bleaching or healing phase.

Results

In general, erythema was seen in a few days, followed by continual scaling during the first week. Erythema and scaling were usually seen continually throughout the bleaching phase. Formation of scales (accumulated horny layers) and itching were also seen in some cases during the second week. After the scales repeatedly came off, improvement of NAC color was usually obtained. Sufficient improvement in NAC color was obtained after a bleaching phase of 4–8 weeks in most cases. During the healing phase, erythema was gradually reduced, while the improvement in NAC color was maintained.

The average treatment period of 15 patients was 16.6 weeks, because some cases underwent the second course. The second treatment course was performed in 4 cases: 2 desired further improvement in color, and 2 were treated for postinflammatory hyperpigmentation on the surrounding mound induced by the first course.

Of 15 patients, HQ-AA ointment was used as an alternative to reduce irritant dermatitis in 2 cases during the bleaching phase and 4 cases during the healing phase, while KA ointment was used in one case during the healing phase. No allergic contact dermatitis to hydroquinone was seen in this study.

The clinical results and the patients' satisfaction were summarized in Table 1. Two patients were evaluated as "excellent," 7 cases as "good," and 3 cases as "fair." No improvement was clinically observed in the other 3 cases. Some improvement was seen in 12 of 15 patients (80.0%).

Six patients achieved sufficient satisfaction with the results, and 5 had slight satisfaction. The other 4 cases were not satisfied with their results. Some satisfaction was recognized by 11 of 15 patients (73.3%).

The representative 4 cases are shown in Figures 1–4.

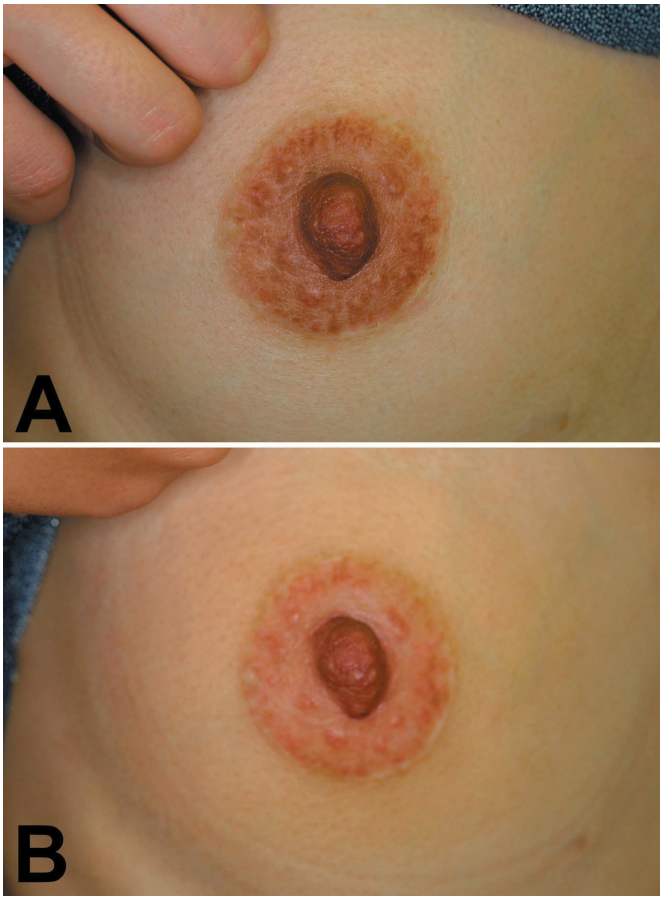

Figure 1. Case 1. A 25-year-old woman who complained about the color of her NAC and some pigmentation of the breast mound underwent the treatment (A: before treatment); 0.2% tretinoin gel was used for 4 weeks together with HQ-LA ointment, followed by application of HQ-LA ointment alone for 4 weeks (B: after treatment of 8 weeks). NAC color was improved though the pigmentation of the breast mound was still observed.

Discussion

It is generally quite difficult to treat disfiguring color of the NAC, so no satisfactory treatment has been reported so far. Laser treatments such as Q-switch ruby laser frequently result in depigmentation and/or scarring (Figure 5). Based on our experiences with an aggressive bleaching treatment using tretinoin and hydroquinone on thousands of patients, the authors applied the modified protocol to treat NAC color, and found it was sufficiently effective. This protocol can eliminate melanin pigmentation quite effectively, although patients experience unpleasant irritant dermatitis, especially in the first 2 weeks. Some of the adverse effects during the bleaching phase can be somewhat suppressed by use of antioxidant lotions, moisturizing lotions/creams, and/or oils. Corticosteroid ointments should not be used in this treatment, the reason for which is mentioned below.

Since Kligman and Willis[3] introduced their depigmenting formula, a number of products based on it, such as Tri-Luma (Galderma Laboratories, Cedex, France), have become commercially available. These products contain tretinoin and hydroquinone along with corticosteroid, and can let patients treat their pigmentation simply and without having severe irritation. However, we believe that corticosteroids reduce not only irritant dermatitis but also depigmenting effects of tretinoin by suppressing keratinocytes proliferation and epidermal turnover. Indeed, based on our initial experiences, simultaneous use of corticosteroids and tretinoin reduced significantly the effectiveness of this treatment. In addition, the separate preparation of tretinoin and hydroquinone is important, because it enables differential use of the two agents with regards to application areas and periods, which is essential in our protocol. We think the critical points of this protocol are: 1 to use a high concentration of tretinoin *aqueous gel*, which means an aggressive and optimal use of tretinoin, 2 to not use corticosteroid at all, 3 to use tretinoin only on the hyperpigmented lesion with a small cotton-tip applicator and use hydroquinone over the large

Table 1. Summarized Data of Clinical Results

	Patient satisfaction			
	Very satisfied	*Slightly satisfied*	*Not satisfied*	*Total*
Excellent	2	0	0	2
Good	4	3	0	7
Fair	0	1	2	3
Poor	0	1	2	3
Total	6	5	4	15

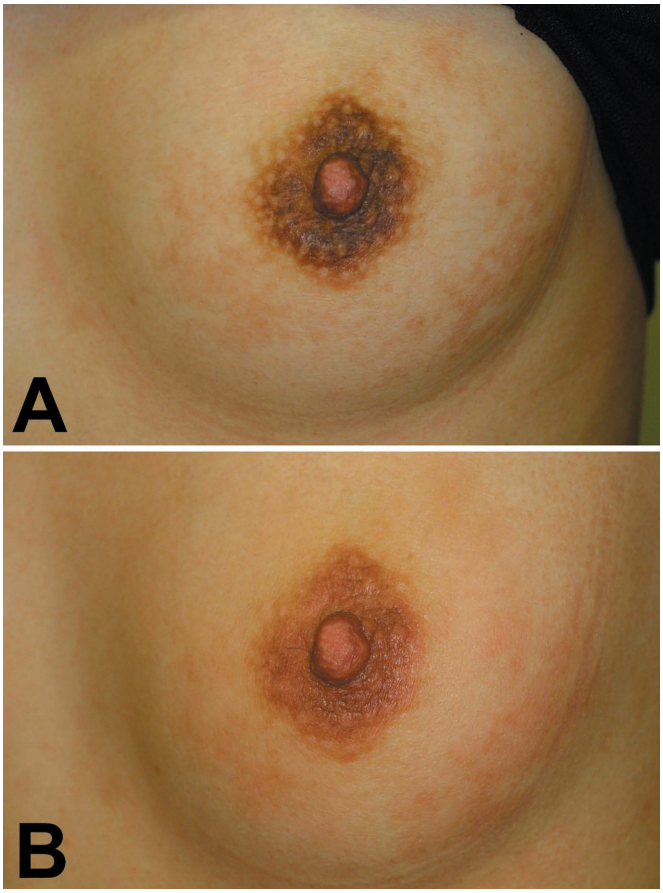

Figure 2. Case 2. A 28-year-old woman underwent the treatment (A: before treatment); 0.2% tretinoin gel was used for 4 weeks together with HQ-LA ointment, followed by application of HQ-LA ointment for 2 weeks and HQ-AA ointments for 4 weeks (B: after treatment of 10 weeks). NAC color was improved, but postinflammatory hyperpigmentation was left on the mound in this case.

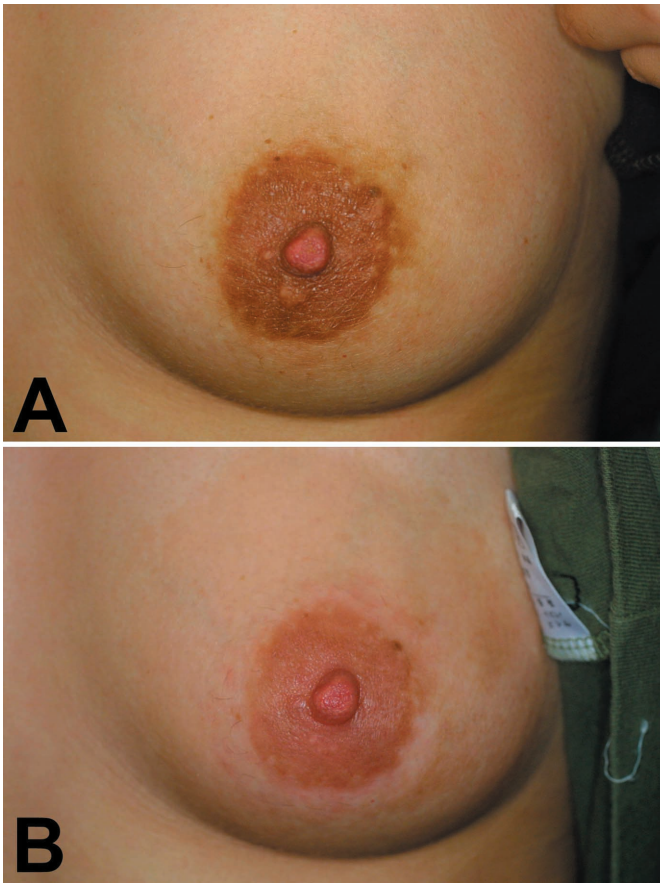

Figure 3. Case 3. A 22-year-old woman underwent the treatment (A: before treatment). Because she underwent mastopexy operation before, she had a linear scar on the areolar margin. 0.2% tretinoin gel was used for 1 week and 0.4% tretinoin for 3 weeks, followed by application of HQ-LA ointment for 6 weeks. (B: after treatment of 10 weeks). NAC color was improved without leaving any postinflammatory hyperpigmentation.

area, including the surrounding area, and 4 to use hydroquinone for at least 4 more weeks after cessation of tretinoin application. The 3rd and 4th points are quite important to avoid postinflammatory hyperpigmentation. Strictly speaking, the optimal amount of tretinoin to administer changes day by day with skin conditions: condition of the stratum corneum, the state of tolerance to tretinoin, and personal variances.

The biological roles of tretinoin and hydroquinone in this treatment should be clearly understood. The authors think that the role of tretinoin in this protocol is to discharge the melanin granules out of the epidermis.[4] Tretinoin can directly accelerate epidermal turnover (promote differentiation of keratinocytes) and indirectly promote the proliferation of keratinocytes. The reason for epidermal hyperplasia after tretinoin application had been unknown, but tretinoin was recently found to promote proliferation of keratinocytes by inducing heparin-binding EGF like growth factor (HB-EGF) secretion from suprabasal keratinocytes.[5–7] These beneficial effects induced by tretinoin are specific for retinoids—they cannot be obtained by chemical peeling agents such as AHA and TCA—and can be greatly suppressed by corticosteroids. The antiretinoid effects of corticosteroids seen in vivo are partly explained by the down-regulation of keratinocyte growth factor expression from dermal fibroblasts induced by corticosteroids.[8]

The role of hydroquinone, on the other hand, is to strongly suppress production of new melanin. This is quite important in the present treatment because tretinoin appears not to suppress new melanogenesis as shown in our previous study using pigmented skin equivalents.[4] According to our experiences, the effectiveness of hydroquinone is far larger than that of

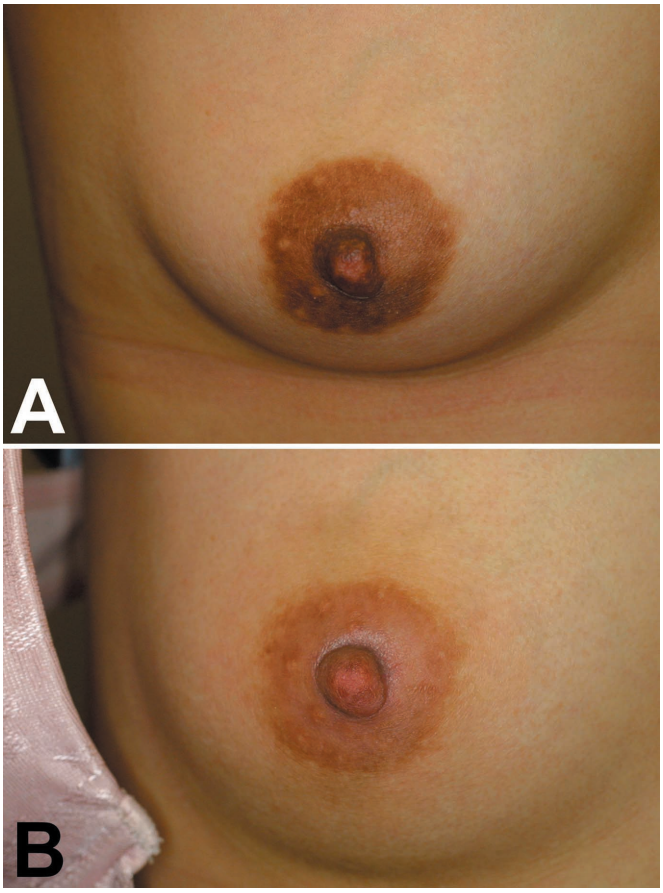

Figure 4. Case 4. A 34-year-old woman underwent the treatment (A: before treatment). Bleaching was performed with 0.2% tretinoin gel and HQ-LA ointment for 6 weeks, and erythema disappeared after 6 weeks of healing phase (B: after treatment of 12 weeks).

kojic acid, which can not necessarily prevent postinflammatory hyperpigmentation induced during the bleaching phase. It is our understanding that application of corticosteroids is not beneficial to avoid postinflammatory hyperpigmentation.

Virtually the only possible complication seen in this study was postinflammatory hyperpigmentation because of irritant dermatitis induced by aggressive use of tretinoin and/or hydroquinone. In our experience, it occurred on breasts more frequently than on faces with the same treatment. Therefore, it may be better to use tretinoin on the area 2–3 mm in from the areola margin, and hydroquinone just on the exact area of the areola. It cannot be denied that pigment darkening could recur after treatment. Daily rubbing of the tissue by undergarments could induce repeated inflammation, followed by postinflammatory hyperpigmentation. Continual application of hydroquinone can prevent this in most cases, or the treatment can be repeated, if desired. Postinflammatory hyperpigmentation could be treated in most cases with HQ-AA ointment in a few months. Tretinoin and hydroquinone, used mildly and carefully, can treat it more quickly.

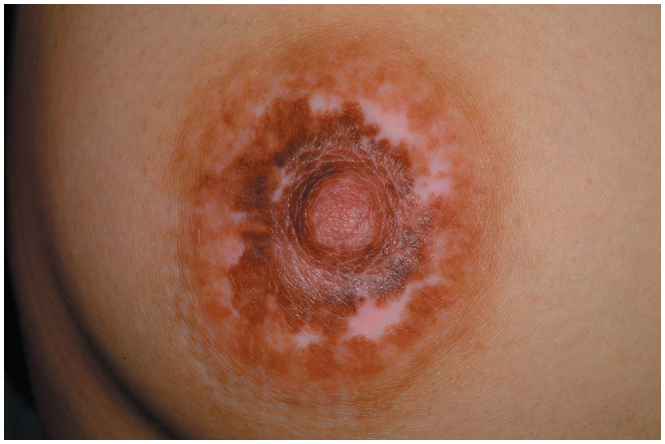

Figure 5. Nipple and areola treated with laser therapy (the type of laser is unknown) sometimes demonstrate white scarring. It is almost impossible to repair the disfiguring appearance.

Conclusions

In the present clinical trials, our protocol improved NAC color without leaving any scars or depigmentation. This is the first report to demonstrate a successful treatment for improvement of NAC color.

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Commentary

This article provides an interesting treatment approach to an area of cutaneous pigmentation sometimes not assessed by dermatologists worldwide. In women of Fitzpatrick skin type III or higher, it is possible to develop increased pigmentation of the nipple-areola complex. Some of this pigmentation may be genetic, but the most common source of this darkening is postinflammatory hyperpigmentation due to the rubbing of undergarments intended to support the breasts. This irritation may be due to the design of the brassiere, but also may be impacted by the construction of the garment and the fabric selected. In the past 2 years, a new area of dermatologic research has been funded by Milliken Company, Spartanburg, SC. This company has given their research and development division the challenge of developing a fabric that decreases cutaneous rubbing friction and prevents maceration as well as new undergarment manufacturing techniques to minimize the irritation caused by fabric seams. The outcome of this research effort has been the development of a new fabric garment line called DermaSense. I mention this as an aside, since many times dermatologists do not consider the effects of clothing on dermatoses of the skin. This article brings to light an important side-effect of clothing friction in a sensitive area of the female body, namely the nipple-areola complex. The authors have applied an approach most commonly used to lighten the skin of the face to the nipple-areola complex. The combination of hydroquinone, a potent melanocyte toxin, with tretinoin gel, an inhibitor of melanin transfer, and lactic acid, a penetration enhancer, functions to ensure an optimal decrease in nipple-areola complex melanization. The authors astutely mention that the hydroquinone must be continued for at least 4 weeks after discontinuation of the tretinoin. The biggest problem in the treatment of postinflammatory hyperpigmentation of this type is recurrence due to continuation of the inciting factor. Fortunately, intense dermatologic research within the fabric industry is leading to new technologies that may be important in a variety of pigmentary and eczematous dermatoses in the near future.

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