A 4% hydroquinone skin care system has been used successfully for many years with tretinoin to help improve the appearance of prematurely photoaged skin.\(^1\) Hydroquinone is effective in reducing hyperpigmentation and melasma,\(^2,3\) and tretinoin can increase the synthesis of collagen and reduce fine wrinkling, mottled hyperpigmentation, and tactile roughness.\(^4,6\)

The combined application of tretinoin and hydroquinone is likely to achieve greater clinical benefit than either agent alone because of their differing mechanisms of action and because tretinoin may facilitate the epidermal penetration of hydroquinone.\(^2\)

Furthermore, their use as part of a coordinated skin care regimen may enhance patient compliance\(^7\)—perhaps because of the convenience of a regimen that defines a daily routine catering not only to the treatment of photodamage but also to overall skin care.
Recently, a version of the hydroquinone system has become available that is specifically designed to be used in conjunction with nonsurgical and nonablative cosmetic procedures (Obagi Condition & Enhance System for Use with Non-Surgical Procedures, Long Beach, California). In addition to hydroquinone, the system contains a cleanser (to remove sebum lipids, desquamated cells, and other debris from the skin), a toner (to remove postcleansing residue and lower the pH of the skin), an exfoliant (to induce sloughing of the stratum corneum), and a sunscreen (to protect against further photodamage). Tretinoin can be added as directed by the physician. To optimize the clinical benefits of each component, the sequence and timing of application of each are clearly defined. Together, the cleanser, toner, and exfoliant may help improve the permeability of the epidermis. Overall, the hydroquinone system plus tretinoin aims to condition the skin before facial rejuvenation procedures, improve the quality of the skin postprocedure, and enhance both clinical outcomes and patient satisfaction.

Applying the hydroquinone system plus tretinoin in conjunction with other facial rejuvenation treatments with different mechanisms of action—such as botulinum toxin type A—should further enhance the degree of clinical improvement. We evaluated the efficacy of the hydroquinone system plus tretinoin as compared to a standard skin care regimen for improving facial appearance in patients who were users of botulinum toxin Type A (BoNT-A) injections.

**METHODS**

**Patients**

Patients were eligible to enroll in this multicenter, randomized, investigator-masked, parallel-group study if they had received at least two upper facial treatments with BoNT-A (Botox COSMETIC; Allergan, Inc., Irvine, California)—one treatment 24 hours before entering the study and one treatment in the previous three to six months. Both BoNT-A treatments were required to have been injected in the same upper facial areas (as treatment for glabellar lines and/or crow’s feet and/or forehead lines) and with a similar number of units. Patients were required to be between 30 and 65 years of age, and patients using any systemic method of birth control must have used it consistently for at least 30 days before the study. Exclusion criteria are shown in Table 1.

**Washout Periods**

The following washout periods were required: seven days for any topical products containing alpha-hydroxy acids, retinoic acid, retinol, salicylic acid, vitamin C, or vitamin D or its derivatives; 30 days for any investigational drug and for facial microdermabrasion (light or medium skin peel); three months for nonablative laser, light, and radiofrequency treatment; and six months for facial dermabrasion (deep skin peel), ablative laser treatments, and dermal filler injections.

**Treatment Regimen**

Patients were randomly assigned (on a one-to-one basis) to use one of the following for 120 days: a 4% hydroquinone skin care system plus 0.05% tretinoin (HS+T) or a standard skin care (SC) regimen. The hydroquinone system plus tretinoin involved applying cleanser, toner, proprietary 4% hydroquinone creams, exfoliant, sunscreen, and 0.05% tretinoin cream (Table 2). The standard skin care regimen involved applying cleanser, moisturizer, and sunscreen (Table 2). The randomization of treatment assignment was in blocks of four, and subject numbers were assigned in ascending order.

Patients were allowed to continue the use of any nonmedicated cosmetics, as long as they were not applied before study visits and their prestudy regimen was otherwise unchanged during the study. No other lotions, creams, powders, or solutions were allowed on the treatment area during the study.

The study (protocol NMM101) was approved by the relevant institutional review boards and conducted in accordance with the 2004 version of the Declaration of Helsinki. All patients gave signed informed consent.

**Outcome Measures**

Investigators graded hyperpigmentation, fine lines/wrinkles, laxity, burning, dryness, peeling, and erythema (as none, trace, mild, moderate, or severe). For burning and dryness, investigators based the grade on the patient’s impression since the last visit. They also evaluated global response to treatment as 100% improvement, ~75% improvement, ~50% improvement, ~25% improvement, no change, or worse.

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**Table 1. Exclusion Criteria**

<table>
<thead>
<tr>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment with botulinum toxin type A just prior to entering the study in an area not previously treated</td>
</tr>
<tr>
<td>History of periorbital surgery, browlift, or related procedures</td>
</tr>
<tr>
<td>Ocular infection, skin disorder around the treated area, marked facial asymmetry, dermatochalasis, deep dermal scarring, or excessively thick sebaceous skin</td>
</tr>
<tr>
<td>Eyelid or eyebrow ptosis</td>
</tr>
<tr>
<td>Use of topical tretinoin in the previous three months, other than the study medication</td>
</tr>
<tr>
<td>History of laser skin resurfacing in the previous six months</td>
</tr>
<tr>
<td>Use of systemic steroid therapy in the previous six months</td>
</tr>
<tr>
<td>Use of an oral retinoid in the previous two years</td>
</tr>
<tr>
<td>Planning of any other facial cosmetic procedure during the study</td>
</tr>
<tr>
<td>Recent excessive exposure to ultraviolet light</td>
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<tr>
<td>Any uncontrolled systemic disease</td>
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</tbody>
</table>

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Patients were asked to evaluate the following: the noticeability of their facial wrinkles, the evenness of their facial color tone, the smoothness of their facial skin, their satisfaction with current treatment, their satisfaction with the overall improvement in their facial appearance, the effect of the study treatment in further enhancing their facial appearance after their latest BoNT-A treatment (a comparison with the effect of past treatment using BoNT-A alone), the proportion of people who have noticed a positive change in their facial appearance by peers, and their facial appearance compared with age.

Table 2. Application Instructions Given to Patients

<table>
<thead>
<tr>
<th>Morning Regimen</th>
<th>Evening Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydroquinone system plus tretinoin</td>
<td>Cleanser—apply to wet the face, rinse thoroughly with lukewarm water, gently pat dry with a soft towel (avoid rubbing the skin with the towel). Toner—apply to entire face using cotton wool, avoiding eye area. Allow to dry. Hydroquinone—apply pea-sized amount in thin film over entire face. Allow to dry. Exfoliant—apply pea-sized amount in thin film over entire face. Wait until absorbed. Sunscreen (SPF 35)—apply to entire face.</td>
</tr>
<tr>
<td>Standard skin care</td>
<td>Cleanser—apply to wet the face, rinse thoroughly with lukewarm water, gently pat dry with a soft towel (avoid rubbing the skin with the towel). Moisturizer—apply to entire face, avoiding the eye area. Allow to dry. Sunscreen—apply to entire face.</td>
</tr>
</tbody>
</table>

Table 3. Scales Used for Patient Evaluations

<table>
<thead>
<tr>
<th>Noticeability of Facial Wrinkles</th>
<th>Evenness of Facial Color Tone</th>
<th>Smoothness of Facial Skin</th>
<th>Satisfaction With Current Treatment</th>
<th>Satisfaction With Overall Improvement in Facial Appearance</th>
<th>Effect of Study Treatment in Further Enhancing Facial Appearance After Botulinum Toxin Type A Treatment*</th>
<th>Noticeability of Positive Change in Facial Appearance by Peers</th>
<th>Facial Appearance Compared With Age</th>
<th>Desire to Continue With Current Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very noticeable</td>
<td>Much more even</td>
<td>Much smoother</td>
<td>Extremely satisfied</td>
<td>Extremely satisfied</td>
<td>Greatly improved</td>
<td>Everyone has noticed a positive change</td>
<td>Much younger</td>
<td>Yes</td>
</tr>
<tr>
<td>Noticeable</td>
<td>More even</td>
<td>Smoother</td>
<td>Satisfied</td>
<td>Satisfied</td>
<td>Improved</td>
<td>A lot of my peers have noticed a positive change</td>
<td>Younger</td>
<td>No</td>
</tr>
<tr>
<td>Slightly noticeable</td>
<td>The same</td>
<td>The same</td>
<td>Indifferent</td>
<td>Indifferent</td>
<td>Somewhat improved</td>
<td>About half of my peers have noticed a positive change</td>
<td>My age</td>
<td>—</td>
</tr>
<tr>
<td>Gone</td>
<td>More uneven</td>
<td>Rougher</td>
<td>Dissatisfied</td>
<td>Dissatisfied</td>
<td>The same</td>
<td>Some of my peers have noticed a positive change</td>
<td>Older</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>—</td>
<td>Much rougher</td>
<td>Very dissatisfied</td>
<td>Very dissatisfied</td>
<td>Worse</td>
<td>No one has noticed a positive change</td>
<td>Much older</td>
<td>—</td>
</tr>
</tbody>
</table>

*A comparison with the effect of past treatment using botulinum toxin type A alone.
of their peers who had noticed a positive change in the patients’ facial appearance, their perception of their facial appearance compared with their age, and their desire to continue with the same treatment after conclusion of the study. The scales for the patient evaluation responses can be seen in Table 3.

**Statistical Analyses**

It was calculated that 30 patients needed to be enrolled in each treatment group (a total of 60 patients) to detect a clinically significant difference in the severity of fine lines/wrinkles (ie, a one-grade difference on the five-point scale) between treatment groups. This assumed a two-sided α of 0.05, a standard deviation of 1.0, power of 95%, and a dropout rate of 10%.

Statistical analyses were performed on all randomized subjects with at least one follow-up visit. Between-group differences were analyzed using a chi-square test for demographic details, Pearson’s chi-square test for the global response to treatment and patient evaluations, and a Student t-test for the other investigator evaluations and for the dose of botulinum toxin type A administered. All statistical tests were two-sided and interpreted at a 5% significance level.

**RESULTS**

**Patients**

A total of 61 patients enrolled in the study (30 assigned to the HS+T group and 31 assigned to the SC group), 55 of whom (90%) completed it. One discontinued due to lack of efficacy (SC group), one discontinued due to personal reasons (SC group), and four were lost to follow-up (two in each group).

The patients had a mean age of 50 years and were predominantly female (98%) and Caucasian (92%), with Fitzpatrick skin Type III (54%). Only the Allergan formulation of BoNT-A was administered; the mean dose that patients had received for their prestudy treatment was 32 ± 12.0 units in the HS+T group and 30 ± 12.0 units in the SC group. There were no significant between-group differences in demographic details, BotNT-A dose, or any of the above-mentioned efficacy or tolerability assessments at baseline.

**Efficacy: Investigator Assessments**

Mean scores for hyperpigmentation and fine lines/wrinkles were significantly lower with the HS+T group than with the SC group as early as Day 30 (p ≤ .05; Figures 1 and 2).

Mean scores for laxity were reduced in the HS+T group (from 1.9 at baseline to 1.3 at Day 120) and increased in the SC group (from 1.5 at baseline to 1.6 at Day 120). Between-group differences in mean laxity scores did not attain statistical significance, but the HS+T regimen was associated with a significantly greater change in score from baseline than the SC regimen at Days 30, 90, and 120 (p ≤ .05).

Overall, the HS+T group was associated with significantly superior global responses to treatment relative to the SC group at all time points (p ≤ .001). Photographic documentation of the effects of treatment with each regimen are shown in Figures 3 and 4.
Mean fine lines/wrinkles score

Day

0 30 60 90 120

Hydroquinone system + tretinoin Standard skin care

Severe

Moderate

Mild

Trace

None

*p ≤ .05, **p ≤ .01 compared with standard skin care

Figure 2. Investigator evaluations of fine lines and wrinkles.

Figure 3. (A) This 48-year-old woman presented for participation in the study and was randomized to receive the hydroquinone skin care system plus tretinoin. (B) One hundred twenty days after beginning treatment. Photographs courtesy of Joel Schlessinger, MD.
Efficacy: Patient Assessments

Overall ratings for all nine of the patient assessments were significantly superior in the HS+T group compared with the SC group at Days 90 and 120 (p ≤ .05).

Between baseline and Day 120, the proportion of patients who considered their facial lines/wrinkles to be noticeable or very noticeable declined from 87% to 21% in the HS+T group and increased from 74% to 81% in the SC group. At Day 120 and compared with standard skin care, there was a considerably greater proportion of patients in the HS+T group who considered the color tone of their skin to be more even or much more even than at baseline (93% vs 8%), considered their facial texture to be smoother or much smoother than at baseline (93% vs 19%), were satisfied or extremely satisfied with their current treatment (93% vs 12%), were satisfied or extremely satisfied with the overall improvement in their facial appearance (89% vs 12%; Figure 5), considered the study treatment to have further enhanced their facial appearance after their latest treatment with BoNT-A (86% vs 8%; Figure 6), and reported that at least some of their peers had noticed a positive change in their facial appearance (82% vs 16%).

Between baseline and Day 120, the proportion of patients who felt that they looked younger or much younger than their age increased from 30% to 64% in the HS+T group and declined from 29% to 23% in the SC group (Figure 7). Overall, 100% of patients in the HS+T group wanted to continue their regimen poststudy, compared with 20% in the SC group.

Tolerability

Mean levels of burning, dryness, peeling, and erythema were significantly greater in the HS+T group than the SC group on Days 30, 60, and 90 and on Day 120 for dryness and peeling (Figures 8-11). Nevertheless, throughout the study, mean levels of burning, dryness, and peeling were

Figure 4. (A) This 54-year-old woman presented for participation in the study and was randomized to receive the standard skin care regimen. (B) One hundred twenty days after beginning treatment. Photographs courtesy of Joel Schlessinger, MD.
less than mild, and mean levels of erythema were less than moderate.

One adverse event was possibly related to the study treatment (a burning sensation from eyebrow waxing in a patient from the HS+T group).

**DISCUSSION**

The results of this study confirm that the adjunctive use of the hydroquinone system plus tretinoin can further enhance facial appearance after botulinum toxin type A treatment—
with significant improvements in fine lines/wrinkles, hyperpigmentation, smoothness of skin, and evenness of skin color tone compared with the application of standard skin care after BoNT-A treatment. These benefits are likely responsible for the significantly greater satisfaction with the overall improvement in facial appearance among those in the HS+T
group, compared with the SC group, after botulinum toxin type A treatment.

Application of the HS + T regimen in combination with BoNT-A treatment has previously been reported in a large-scale experience trial in which various assessments of skin quality were evaluated using a four-point scale, ranging from none to severe/prominent. The incidence of patients showing at least a one-grade improvement from baseline in these assessments after treatment with the hydroquinone system, tretinoin, and BoNT-A was 83% for hyperpigmentation, 82% for tactile roughness, 82% for periocular fine wrinkles, 80% for sallowness, 65% for perioral fine wrinkles, and 18% for erythema. The incidence of patients achieving at least a two-grade improvement from baseline was 33% for hyperpigmentation, 34% for tactile roughness, 30% for periocular fine wrinkles, 27%

Figure 9. Investigator evaluations of dryness based on patient reports.

Figure 10. Investigator evaluations of peeling.
for sallowness, 15% for perioral fine wrinkles, and 3% for erythema.9 As the improvements in hyperpigmentation, tactile roughness, and sallowness would not be anticipated from the botulinum toxin, it was concluded that the combined HS + T treatment helped to optimize the overall aesthetic improvement across multiple parameters of skin quality. The use of different facial rejuvenation treatments with complementary modes of action can thus enhance clinical improvement and, ultimately, lead to increased patient satisfaction.10,11 Indeed, for many patients, combination therapy is the ideal approach to treatment, as it can target different areas of the face and different manifestations of aging or photoaging, including both static and dynamic changes.

Many combination therapies have been utilized to enhance the appearance of the skin. The adjunctive use of hydroquinone plus tretinoin has been reported to enhance clinical outcomes achieved after intense pulsed light therapy.12 Other treatments reported to have been used in combination with both hydroquinone and tretinoin include Q-switched ruby laser therapy13,14 and dermabrasion.15 Similarly, the adjunctive use of BoNT-A has been reported to enhance the clinical improvement attained with intense pulsed light,16,17 collagen and hyaluronic acid fillers,11,18 and chemabrasion (trichloroacetic acid followed by dermasanding).19 Other treatments reported to have been used in combination with BoNT-A include chemical peels20 and fractional resurfacing.21

One strength of this study was the number of evaluations regarding the patients’ own perceptions; the patients are the ultimate judge of the success of any cosmetic treatment, and so their perceptions are one of the most important outcome end points. A potential weakness of this study was that patients had to recall the level of improvement attained after their first botulinum toxin treatment to judge whether the HS + T treatment resulted in additional improvements after their second botulinum toxin treatment. However, as the botulinum toxin and the topical treatment affected different aspects of photodamage, the accuracy of recollections of such qualitative differences may have been affected less than if the recollections had been more heavily reliant on quantitative differences. Although a split-face study design might have avoided the risks associated with a memory-dependent parameter, the added complexity for patients of adhering to different topical regimens on either side of their face might have caused confusion and impaired compliance.

**CONCLUSIONS**

Compared with standard skin care, the hydroquinone system plus tretinoin offers multiple significant clinical benefits for users of BoNT-A—including improvements in fine lines/wrinkles, hyperpigmentation, smoothness of skin, and evenness of skin color tone. It also offers a relatively greater likelihood of patients reporting that their topical study treatment further enhanced facial appearance after BoNT-A treatment and a relatively greater likelihood of patients perceiving themselves to look younger than their actual age. Finally, application of the hydroquinone system plus tretinoin offers greater patient satisfaction than standard skin care, with a correspondingly high proportion of patients motivated to continue with their treatment after the end of the study.

**Disclosures**

All authors are investigators for Obagi Medical Products (OMP), Inc. Dr. Schlessinger is a consultant, adviser to, and shareholder in OMP, Inc. Dr. Kenkel has received past research
grants from Ulthera, Ethicon Endosurgery, Lumenis, and Allergan. He has also received equipment for research from Lumenis, Sciton, and Eclipse. He has dissociated from previous advisory roles with Ultrasound, Ethicon, and Ethicon Endosurgery. Dr. Werschler is a consultant, investigator, speaker for, and/or investor in Allergan, Bioform/Mierz, Excalliant, Galderma, Medicis, MyoScience, Pacific Bioscience, SkinMedica, Stiefel, and sanofi-aventis.

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This study was supported by Obagi Medical Products (OMP), Inc., Long Beach, CA. The study protocol was designed by the investigators in conjunction with OMP, Inc. The study data were collected by the investigators and analyzed by an independent clinical research organization. The writing of the manuscript was outsourced by the study sponsor to an independent medical communications company, and the data were interpreted by the medical writer involved in the development of the manuscript. The decision to submit the report for publication was made jointly by the study sponsor and all investigators.

REFERENCES

18. Carruthers J, Carruthers A. A prospective, randomized, parallel group study analyzing the effect of BTX-A (Botox) and nonanimal sourced hyaluronic acid (NSHA, Restylane) in combination compared with NSHA (Restylane) alone in severe glabellar rhytides in adult female subjects: treatment of severe glabellar rhytides with a hyaluronic acid derivate compared with the derivate and BTX-A. *Dermatol Surg* 2003;29:802-809.