

FURTHER ENHANCEMENT OF FACIAL APPEARANCE WITH A HYDROQUINONE/TRETINOIN SKIN CARE SYSTEM IN PATIENTS PREVIOUSLY TREATED WITH BOTULINUM TOXIN TYPE A: A MULTICENTER INVESTIGATOR-MASKED STUDY

Joel Schlessinger, MD
Skin Specialists, PC,
Omaha, NE

Phillip Werschler, MD
Premier Clinical Research,
Spokane, WA

Jeffrey Kenkel, MD, FACS
University of Texas
Southwestern,
Dallas, TX

INTRODUCTION

A 4% hydroquinone/tretinoin skin care system has been used successfully for many years to help improve the appearance of prematurely photoaged skin.¹ Hydroquinone can decrease the visible damage due to hyperpigmentation and melasma,² and tretinoin can reduce fine wrinkling, mottled hyperpigmentation, and tactile roughness.³⁻⁹ Because of their different mechanisms of action, and because tretinoin may facilitate the epidermal penetration of hydroquinone,² their combined use is likely to achieve greater clinical benefits than either agent alone. Furthermore, their use in an acne system providing a coordinated skin care regimen may enhance patient compliance⁶—perhaps because of the convenience of using a system that defines a daily routine to cater not only to acne treatment but also to overall skin care.

Recently, a version of the hydroquinone/tretinoin system that is specifically designed to be used in conjunction with non-surgical and non-ablative procedures has become available.⁷ In addition to hydroquinone and tretinoin, the system contains a cleanser (to remove sebum lipids, desquamated cells, and other debris from the skin), a toner (to remove post-cleansing residue and lower the pH of the skin), an exfoliant (to produce sloughing of the stratum corneum), and a sunscreen (to protect against further photodamage). In order to optimize the clinical benefits of each component, the sequence and timing of application of each is defined. Together, the cleanser, toner, and exfoliant may help improve the permeability of the epidermis. Overall, the system aims to condition the skin before facial rejuvenation procedures, enhance the quality of the skin post-procedure, and enhance both clinical outcomes and patient satisfaction.

Using the hydroquinone/tretinoin system 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 attainable. We sought to evaluate the efficacy of the hydroquinone/tretinoin system, compared with a standard skin care regimen, in improving facial appearance in patients who were users of botulinum toxin type A.

METHODS

Study design

- Multicenter, randomized, investigator-masked, parallel-group study

Main inclusion criteria

- A minimum of two previous upper facial treatments with botulinum toxin type A:
 - One 24 hours before entering the study and one in the previous 3-6 months
 - Both in the same upper facial areas (to treat glabellar lines and/or crow's feet and/or forehead lines)
- Both with the same formulation and a similar number of units.
- 30-65 years of age

Main exclusion criteria

- History of periorbital surgery, brow lift, or related procedures
- Ocular infection, skin disorder around the treated area, marked facial asymmetry, dermatochalasis, deep dermal scarring, or excessively thick sebaceous skin
- Eyelid or eyebrow ptosis
- History of laser skin resurfacing in the previous 6 months
- Use of topical tretinoin in the previous 3 months other than the study medication
- Use of systemic steroid therapy in the previous 6 months
- Use of an oral retinoid in the previous 2 years
- Planning of any other facial cosmetic procedure during the study
- Recent excessive exposure to ultraviolet light
- Any uncontrolled systemic disease

Washout periods

- 7 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)
- 3 months for non-ablative laser, light, and radiofrequency treatment
- 6 months for facial dermabrasion (deep skin peel), ablative laser treatments, and injection of a dermal filler

Treatment regimen

- Random assignment (1:1) to one of the following (Table 1) for 120 days:
 - 4% hydroquinone/0.05% tretinoin skin care system, comprising:
 - Cleanser

- Toner
- Proprietary 4% hydroquinone
- Exfoliant
- Sunscreen
- 0.05% tretinoin cream

- Standard skin care regimen, comprising:

- Cleanser
- Moisturizer
- Sunscreen

- The use of any non-medicated cosmetics could be continued as long as they were not applied before any study visit and their pre-study regimen was otherwise unchanged during the study. No other lotions, creams, powders, or solutions were allowed on the treatment area during the study.

Outcome measures

- Investigator evaluations (rated as none, trace, mild, moderate, or severe):
 - Hyperpigmentation
 - Fine lines/wrinkles
 - Laxity
 - Burning
 - Dryness
 - Peeling
 - Erythema

TABLE 1 Application instructions for each study regimen.

Treatment regimen	Morning regimen	Evening regimen
Hydroquinone/tretinoin system	<p>Cleanser - apply to wet the face, rinse thoroughly with lukewarm water, gently pat dry with a soft towel (avoiding rubbing the skin with the towel).</p> <p>Toner - apply to entire face using cotton wool, avoiding eye area. Allow to dry.</p> <p>Hydroquinone - apply pea-sized amount in thin film over entire face. Allow to dry.</p> <p>Exfoliant - apply pea-sized amount in thin film over entire face. Wait until absorbed.</p> <p>Sunscreen (SPF 35) - apply to entire face.</p>	<p>Cleanser - apply to wet the face, rinse thoroughly with lukewarm water, gently pat dry with a soft towel (avoiding rubbing the skin with the towel).</p> <p>Toner - apply to entire face using cotton wool, avoiding the eyes. Allow to dry.</p> <p>Hydroquinone - apply pea-sized amount in thin film over entire face. Allow to dry.</p> <p>Hydroquinone (different formulation to that used in previous step) - apply pea-sized amount in thin film over entire face.</p> <p>Tretinoin - apply pea-sized amount in thin film over entire face. Allow to dry before retiring to bed.</p>
Standard skin care	<p>Cleanser - apply to wet the face, rinse thoroughly with lukewarm water, gently pat dry with a soft towel (avoiding rubbing the skin with the towel).</p> <p>Moisturizer - apply to entire face, avoiding the eye area. Allow to dry.</p> <p>Sunscreen - apply to entire face.</p>	<p>Cleanser - apply to wet the face, rinse thoroughly with lukewarm water, gently pat dry with a soft towel (avoiding rubbing the skin with the towel).</p> <p>Moisturizer - apply to entire face, avoiding the eye area. Allow to dry.</p>

TABLE 2 Scales for patient evaluations.

Noticeability of facial wrinkles	Evenness of facial color tone	Smoothness of facial skin	Satisfaction with current treatment	Satisfaction with overall improvement in facial appearance	Improvement compared with previous botulinum toxin type A treatments	Notice of positive change in facial appearance by peers	Facial appearance compared with age	Desire to continue with current treatment
Very noticeable	Much more even	Much smoother	Extremely satisfied	Extremely satisfied	Greatly improved	Everyone has noticed a positive change	Much younger	Yes
Noticeable	More even	Smoother	Satisfied	Satisfied	Improved	A lot of my peers have noticed a positive change	Younger	No
Slightly noticeable	The same	The same	Indifferent	Indifferent	Somewhat improved	About half of my peers have noticed a positive change	My age	—
Gone	More uneven	Rougher	Dissatisfied	Dissatisfied	The same	Some of my peers have noticed a positive change	Older	—
—	—	Much rougher	Very dissatisfied	Very dissatisfied	Worse	No one has noticed any positive changes	Much older	—

- Patient evaluations (Table 2):
 - Noticeability of facial wrinkles
 - Evenness of facial color tone
 - Smoothness of facial skin
 - Satisfaction with current treatment
 - Satisfaction with overall improvement in facial appearance
 - Effect of study treatment in further enhancing facial appearance after the latest botulinum toxin type A treatment (a comparison with the effect of past treatment using botulinum toxin type A alone)
 - Notice of positive change in facial appearance by peers
 - Facial appearance compared with age
 - Desire to continue with study treatment.

Statistical analyses

- Between-group differences were analyzed using the following tests:
 - Chi-square test for demographic details
 - Student's t test for the investigator evaluations and for the dose of botulinum toxin type A
 - Pearson's chi-square test for the patient evaluations.
- A P value of ≤ 0.05 was considered statistically significant.

RESULTS

Patients

- A total of 61 patients enrolled and 55 (90%) completed:
 - 1 discontinued due to lack of efficacy (standard skin care group)
 - 1 discontinued due to personal reasons (standard skin care group)
 - 4 were lost to follow-up (2 in each group).
- Mean age of 50 years.
- Predominantly:
 - Female (98%)
 - Caucasian (92%)
 - Fitzpatrick skin type III (54%).
- There were no significant between-group differences in demographic details or botulinum toxin type A dose.

Efficacy – investigator assessments

- Mean scores for hyperpigmentation and fine lines/wrinkles were significantly lower with the hydroquinone/tretinoin treatment than with standard skin care as early as day 30 ($P \leq 0.05$, Figures 1 and 2).
- Mean laxity scores were reduced with the hydroquinone/tretinoin treatment (from 1.9 at baseline to 1.3 at day 120) and increased with the standard skin care regimen (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 hydroquinone/tretinoin treatment was associated with a significantly greater change in score from baseline than the standard skin care regimen at days 30, 90, and 120 ($P \leq 0.05$).

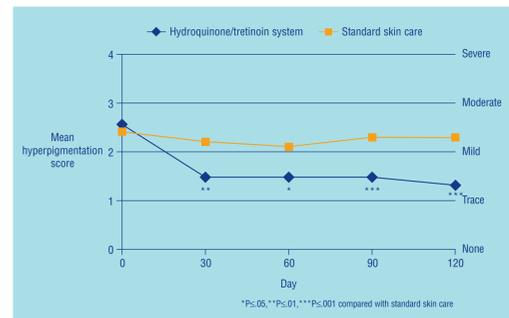


Figure 1. Hyperpigmentation.

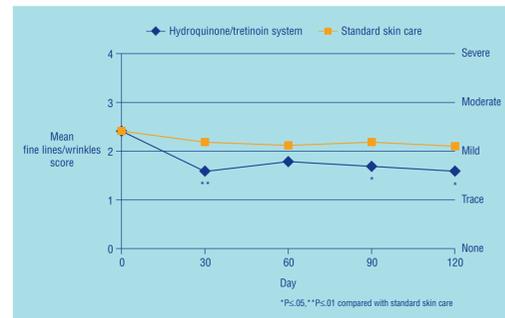


Figure 2. Fine lines and wrinkles.

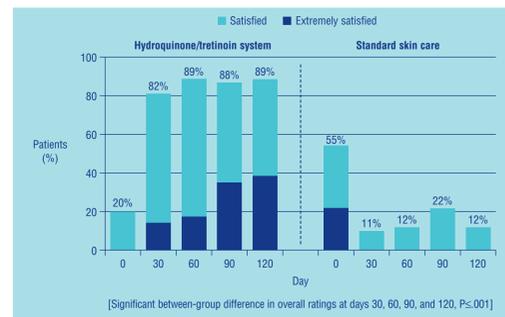


Figure 3. Patient satisfaction with overall improvement in facial appearance.

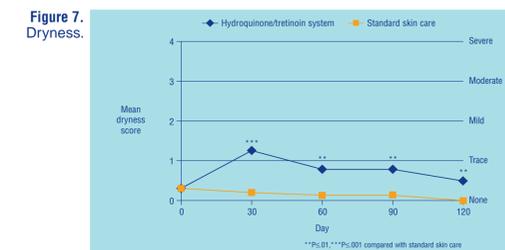
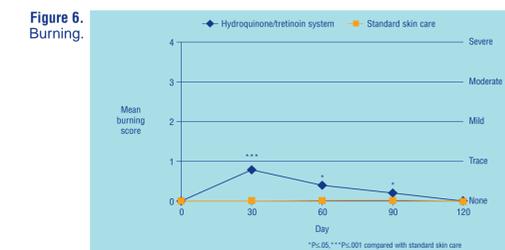


Figure 7. Dryness.

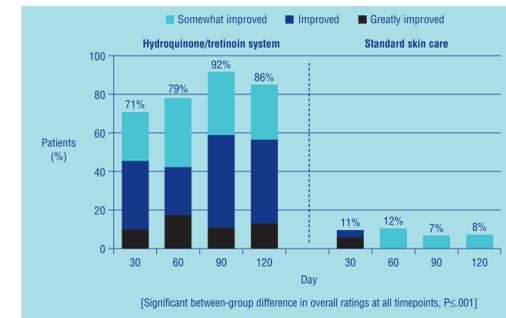


Figure 4. Effect of study treatment in further enhancing facial appearance after botulinum toxin type A treatment (a comparison with the effect of past treatment using botulinum toxin type A alone).

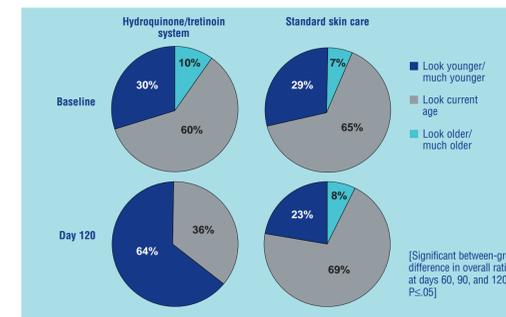


Figure 5. Patient evaluation of facial appearance compared to age.

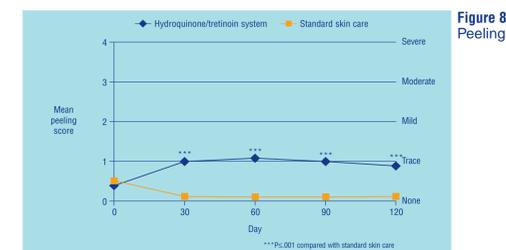


Figure 8. Peeling.

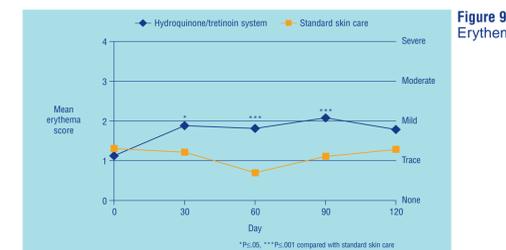


Figure 9. Erythema.

Efficacy – patient assessments

- Overall ratings for all nine of the patient assessments reported were significantly superior in the hydroquinone/tretinoin group compared with the standard skin care group at days 90 and 120 ($P \leq 0.05$). (There had been no significant between-group differences in these parameters at baseline.)
- 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 hydroquinone/tretinoin group
 - Increased from 74% to 81% in the standard skin care group.
- At day 120, and compared with standard skin care, there was a considerably greater proportion of patients in the hydroquinone/tretinoin 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 study treatment (93% vs. 12%)
 - Were satisfied or extremely satisfied with the overall improvement in their facial appearance (89% vs. 12%) (Figure 3)
 - Considered their study treatment further enhanced facial appearance after their latest botulinum toxin type A treatment (86% vs. 8%) (Figure 4)
 - 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 considered that they looked younger or much younger than their age (Figure 5):
 - Increased from 30% to 64% in the hydroquinone/tretinoin group
 - Declined from 29% to 23% in the standard skin care group.
- Overall, 100% of patients in the hydroquinone/tretinoin group wanted to continue their regimen post-study compared with 20% in the standard skin care group.

Tolerability

- Throughout the study, mean levels of burning, dryness, and peeling were less than mild, and mean levels of erythema were less than moderate (Figures 6-9). Mean levels of burning, dryness, peeling, and erythema were significantly greater with the hydroquinone/tretinoin regimen than with standard skin care on days 30, 60, and 90, and on day 120 for dryness and peeling.
- One adverse event was possibly related to study treatment (a burning sensation from eyebrow waxing in a patient receiving hydroquinone/tretinoin treatment).

CONCLUSIONS

Compared with standard skin care, the hydroquinone/tretinoin system offers multiple significant clinical benefits in users of botulinum toxin type 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 considering their topical study treatment further enhanced facial appearance after botulinum toxin type A treatment and a relatively greater likelihood of patients perceiving themselves to look younger than their actual age. Finally, use of the hydroquinone/tretinoin system offers greater patient satisfaction and a high proportion of patients motivated to continue with their treatment after the first 4 months of therapy.

REFERENCES

- Hemdon JH, Stephens TJ, Sigler ML. Efficacy of a tretinoin/hydroquinone-based skin health system in the treatment of facial photodamage. *Cos Derm* 2006;19:255-62.
- Halder RM, Richards GM. Topical agents used in the management of hyperpigmentation. *Skin Therapy Lett* 2004;9:1-3.
- Renova® (tretinoin emollient cream) 0.05% prescribing information. OrthoNeutrogena website. <https://www.aboutrenova.com/RENOVA.05.pdf>. Published February 1998. Accessed May 14, 2009.
- Kang S, Bergfeld W, Gottlieb AB, et al. Long-term efficacy and safety of tretinoin emollient cream 0.05% in the treatment of photodamaged facial skin: a two-year, randomized, placebo-controlled trial. *Am J Clin Dermatol* 2005;6:245-53.
- Griffiths CE. The role of retinoids in the prevention and repair of aged and photoaged skin. *Clin Exp Dermatol* 2001;26:613-8.
- Bowe WP, Shalita AR. Effective over-the-counter acne treatments. *Semin Cutan Med Surg* 2008;27:170-6.
- Obagi Medical Products website. Obagi Medical Products launches two new systems to optimize results of non-surgical and surgical facial aesthetic procedures [press release, Aug 22, 2007]. <http://phx.corporate-ir.net/phoenix.zhtml?c=124836&p=irol-newsArticle&D=1042623&highlight=>. Accessed May 27, 2009.

DISCLOSURE

Supported by OMP, Inc., Long Beach, CA.