

**Benefits of Using a 4% Hydroquinone Skin Care System Plus Tretinoin
Adjunctively with OnabotulinumtoxinA and a Hyaluronic Acid Filler for Facial
Rejuvenation: A Pilot Study**

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Introduction

Aging and photodamage can result in multiple deleterious changes to facial skin including dyspigmentation, wrinkling, tactile roughness, and laxity. No one treatment option for facial rejuvenation is effective against all aspects of photodamage—so combination therapy is generally required for optimal results.

The most commonly performed cosmetic procedures in 2010 involved injecting botulinum toxin type A or hyaluronic acid filler; these accounted for approximately 41% and 9% of such procedures, respectively.¹ Both treatments can help to reduce the appearance of wrinkles and, as they have different mechanisms of action, their actions are complementary. Botulinum toxin inhibits the contraction of facial muscles that cause movement-associated wrinkles whereas hyaluronic acid fillers help to add volume to the skin and can reduce the appearance of folds and wrinkles that are not necessarily related to facial movement. However, although both can be highly effective in reducing

wrinkling, neither has any effect on hyperpigmentation which is often an important component of photodamage.

Hydroquinone (HQ) and tretinoin are both known to be effective in reducing hyperpigmentation and, in addition, tretinoin can reduce fine wrinkling and skin roughness.^{2,3} Therefore, combination therapy utilizing these topical treatments adjunctively with botulinum toxin and hyaluronic acid would be expected to offer efficacy against three major components of photodamage—hyperpigmentation, wrinkling, and skin roughness.

The combined use of HQ and tretinoin is likely to achieve greater clinical benefits than either agent alone not only because they have different mechanisms of action but also because tretinoin may help enhance HQ penetration through the stratum corneum and protect HQ from oxidation.^{4,5} Furthermore, using both agents in a coordinated skin care regimen including, for example, a cleanser and toner may enhance efficacy still further as it appears that such regimens may enhance patient compliance⁶ and, potentially therefore, efficacy. This is perhaps because patients appreciate the convenience of using a single regimen that caters not only for the treatment of photodamage but also for overall skin care. A 4% HQ treatment system is available that has been designed for use in conjunction with tretinoin cream specifically in patients undergoing non-surgical and non-ablative cosmetic procedures.⁷ It is rational to anticipate that combination therapy utilizing this 4% HQ treatment system, tretinoin cream, botulinum toxin type A, and a

hyaluronic acid filler could be highly effective in mitigating the effects of aging and photoaging on facial skin.

Methods

Study design

- Two-center, open-label, single-group, pilot study

Main inclusion criteria

- 35-65 years old
- Evidence of photoaging—Glogau type 2 (wrinkles in motion) or 3 (wrinkles at rest)
- Planning to receive facial rejuvenation treatments with injections of:
 - OnabotulinumtoxinA⁸
 - Hyaluronic acid⁹ (non-animal sodium hyaluronate with 0.3% lidocaine)
- Expected to achieve cosmetically significant benefit from the filler and onabotulinum toxin injections in the opinion of the investigator

Main exclusion criteria

- Recent excessive facial exposure to ultraviolet light
- Any skin condition that might interfere with diagnosis or evaluations
- Recent alcohol or drug abuse
- Uncontrolled systemic disease

Washout periods

- 1 month for microdermabrasion and investigational drugs
- 6 weeks for topical use of retinoids, HQ, vitamin C and/or D preparations, and medicated creams, lotions, powders etc.
- 3 months for laser/light therapies and botulinum toxins
- 6 months for dermal fillers

Treatment regimen

- OnabotulinumtoxinA and hyaluronic acid injections were given according to the investigator's standard of care and the individual needs of each patient, with the only restriction being the maximum dosage allowed:
 - 50 U for onabotulinumtoxinA
 - 2 mL for hyaluronic acid.
- Patients were instructed to then apply the 4% HQ skin care system plus tretinoin cream on their face for 12 weeks as detailed in Table 1.
- The concentration of tretinoin was at the discretion of the investigator depending on their standard of care and individual patient characteristics. It could also be altered during the study at the discretion of the investigator.

Evaluations

- Study staff reviewed procedures and examined the study products that patients brought back at visits, and then estimated each patient's compliance as not compliant (<50%), mostly compliant (50-74%), or very compliant (75-100%). <<**Note protocol**

had categories of 50-75% and 75-100%. Have changed this to 50-74% and 75-100% so is clear which category 75% belongs in. If incorrect, please advise>>

- Investigator evaluations (Table 2):
 - Global evaluation
 - Aesthetic improvement
 - Dyschromia, hyperpigmentation, tactile roughness, fine lines/wrinkles, laxity, telangiectasia, erythema, and peeling
- Patient evaluations:
 - Burning, dryness, and tenderness (Table 2)
 - Appearance of skin, improvement in skin tone, improvement in skin texture, and fewer fine lines and wrinkles (rated as improved, moderately improved, or extremely improved).

Statistical analyses

- Within-group changes from baseline in the score for dyschromia, hyperpigmentation, tactile roughness, fine lines/wrinkles, laxity, telangiectasia, erythema, peeling, burning, dryness, and tenderness were analyzed using the Wilcoxon signed-rank test.

Results

Patients

- Of 27 female patients enrolled, 100% completed.
- Mean age was 44 years (\pm SD of 10.7).
- Predominantly Caucasian:

- 52% Caucasian
 - 22% Hispanic
 - 15% Black
 - 11% Asian.
- Predominantly Fitzpatrick skin type III or IV:
 - I (4%)
 - II (19%)
 - III (33%)
 - IV (30%)
 - V (15%).
- Mean volume of hyaluronic acid filler injected = 1.9 mL (\pm SD of 0.39).
- Mean dose of onabotulinumtoxinA injected = 37 U (\pm SD of 13.9).

Patient compliance

- At week 6:
 - 27 (100%) subjects were “very compliant (75-100%)”.
- At week 12:
 - 25 (93%) were “very compliant (75-100%)”
 - 1 (4%) were “mostly compliant (50-74%)”
 - 1 (4%) had missing data.

Investigator evaluations of efficacy

- 100% of patients showed both global improvement and aesthetic improvement at weeks 6 and 12 (Figures 1 and 2).
- At least a 1-point improvement was reported at week 12 (Figure 3) for:
 - Dyschromia in 85% of patients
 - Hyperpigmentation in 82% of patients
 - Tactile roughness in 74% of patients
 - Fine lines/wrinkles in 37% of patients
 - Laxity in 19% of patients.
- Dyschromia, hyperpigmentation, fine lines/wrinkles, and tactile roughness scores were significantly reduced from baseline at weeks 6 and 12 ($P < .05$). Between baseline and week 12, median grades declined from:
 - “Multiple small or medium brown spots” → “few small brown/tan spots” for dyschromia
 - Mild → trace for hyperpigmentation
 - Mild → trace for fine lines/wrinkles
 - Trace → none for tactile roughness.
- Median scores for laxity and telangiectasia were unchanged.

Patient evaluations of efficacy

- As shown in Figure 4, 100% of patients reported improvements at week 12 in the:
 - Appearance of their skin
 - Skin tone
 - Skin texture

- Number of fine lines and wrinkles.

Tolerability

- Two subjects (7%) reported adverse events that were at least probably related to treatment, and these resolved without sequelae with continued treatment:
 - Moderate bruising (n = 1)
 - Mild redness and moderate peeling (n = 1).
- Although erythema and tenderness scores were transiently statistically significantly higher than baseline at week 6, median scores did not exceed trace levels and so these changes were unlikely to be clinically significant.
- Similarly, dryness and peeling scores were statistically significantly higher than baseline at weeks 6 and 12 but median scores did not exceed trace levels and so these changes were unlikely to be clinically significant.
- There were no significant changes from baseline in scores for burning.

Conclusions

In this pilot study involving combination therapy with a 4% HQ system, tretinoin cream, onabotulinumtoxinA, and a hyaluronic acid filler, aesthetic improvement was achieved in 100% of patients according to both investigator and patient evaluations. More specifically, significant reductions from baseline were reported in the levels of dyschromia, hyperpigmentation, fine lines/wrinkles, and tactile roughness.

Patients undergoing facial rejuvenation treatment with botulinum toxin type A and/or a dermal filler may benefit from adjunctive use of the 4% HQ system plus tretinoin cream. This topical treatment is generally well tolerated and offers improvements in dyschromia, hyperpigmentation, and tactile roughness that would not be expected from botulinum toxin and filler treatment alone—thus enhancing overall aesthetic improvement and, potentially, patient satisfaction.

References

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Disclosures

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Table 1. Topical regimen (4% HQ skin care system plus tretinoin cream).

Component of topical regimen	Application
4% HQ skin care system, consisting of 6 proprietary products:	
1. Foaming gel cleanser (containing aloe barbadensis leaf juice)	Twice daily
2. Toner (containing aloe barbadensis leaf juice and witch hazel)	Twice daily
3. 4% HQ	Twice daily
4. Exfoliation enhancer (containing glycolic acid and lactic acid)	Each morning
5. Sunscreen SPF 35	Each morning
6. 4% HQ (different formulation to above-mentioned 4% HQ)	Each evening
Tretinoin cream (concentration at discretion of investigator)	Each evening

<<OBAGI – PLEASE CONFIRM THE TWO 4% HQ PRODUCTS MENTIONED IN THIS TABLE (PRODUCTS #3 and 6 – i.e. “CLEAR” AND “BLENDER”) ARE DIFFERENT FORMULATIONS TO EACH OTHER. IF NOT, WILL NEED TO AMEND TEXT HERE>>

Table 2. Scales used to evaluate tolerability parameters.

Score	Global evaluation	Aesthetic improvement	Dyschromia	Hyperpigmentation, tactile roughness, fine lines and wrinkles, laxity, telangiectasia, erythema, peeling	Burning, dryness, tenderness
-1	—	Worse	—	—	—
0	Completely cleared	No change	None	None (normal)	None (normal, no discomfort)
1	Almost cleared (~90% improvement)	Mild improvement	Few small brown/tan spots	Trace (barely visible and localized)	Trace (an awareness, but no discomfort and no intervention required)
2	Marked improvement (~75% improvement)	Moderate improvement	Multiple small or medium brown spots	Mild (somewhat visible and diffuse)	Mild (a noticeable discomfort that causes intermittent awareness)
3	Moderate improvement (~50% improvement)	Marked improvement	Multiple large brown spots	Moderate (visible and diffuse)	Moderate (a noticeable discomfort that causes continuous awareness)
4	Mild improvement (~25% improvement)	—	Numerous brown spots throughout	Severe (extremely visible and dense)	Severe (a definite continuous discomfort that interferes with normal daily activities)
5	No change	—	—	—	—
6	Exacerbation	—	—	—	—

Figure 1. Investigator evaluation of global and aesthetic improvements.

Figure 2. Improvements from baseline at week 12.

Figure 3. Investigator evaluation of improvements in various manifestations of photodamage.

Figure 4. Percentage of patients reporting improvements in their skin at week 12.