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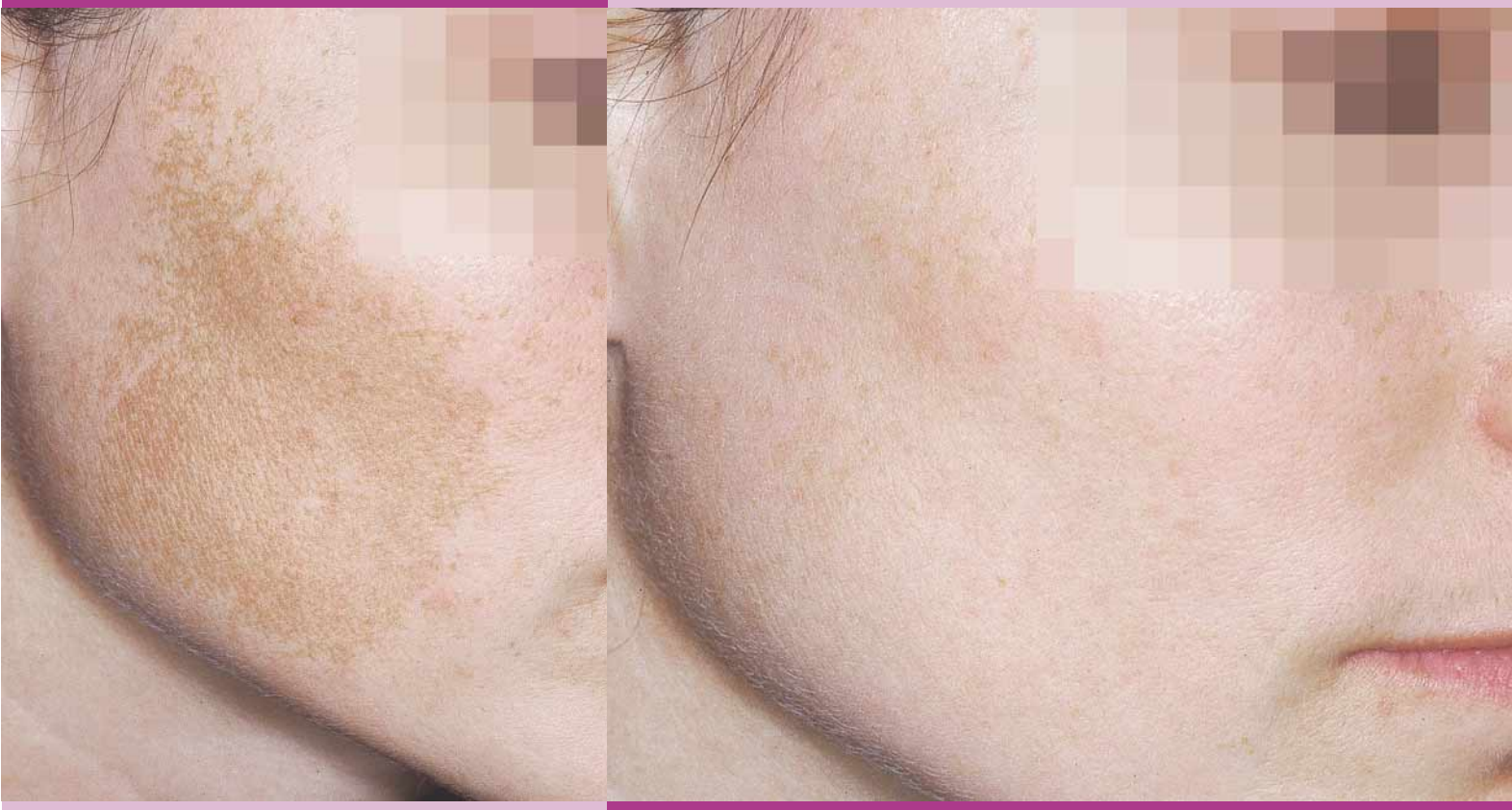
New Directions in the Treatment of Melasma



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Melasma and the Challenges of Treating Skin of Color

Leslie S. Baumann, MD

Melasma, frequently called chloasma or the mask of pregnancy, is an acquired macular hyperpigmentation that most often occurs on the face. Ninety percent of those affected are women, and it is more common in darker skin types, particularly African Americans, Asians, and Hispanics.[1] The American Academy of Dermatology estimates that 5 million to 6 million American women, most of them between 20 and 39 years of age, have melasma. Although cosmetic, melasma is nonetheless a source of stress and embarrassment to those who have it. It is a condition physicians find frustrating because it can be difficult to treat.

Melasma presents as irregular patches of pigmentation ranging in color from light to dark brown and is most commonly found over the centrofacial region, comprising the cheeks, forehead, upper lip, nose and chin.[2] There are three major histological types of melasma—epidermal, dermal, and mixed. In epidermal melasma, the most common type, melanin is concentrated in the basal, suprabasal, and stratum corneum layers. When the patient's skin is examined under a Wood's light, epidermal melasma appears darker and with more pronounced lesions. Dermal melasma, in which melanin-filled macrophages are present in a perivascular distribution in the superficial and middle dermis, appears less visible under a Wood's light. The epidermal type responds to treatment, but there is currently no effective therapy for the dermal type. The mixed type contains an epidermal component, which causes it to fluoresce under the Wood's light, possibly leading to it being misdiagnosed as epidermal. Patients with the mixed-type melasma may see some improvement as the epidermal component responds to treatment.

Estrogen, UV Light Are Chief Causative Factors

The precise etiology of melasma is poorly understood; however, exposure to ultraviolet (UV) radiation or visible light appears to be a precipitating factor. Because melasma most often appears in women who are pregnant or using oral contraceptives, estrogen is thought to play a role. Recent studies have suggested that estradiols, particularly 17 beta-estradiol, are important. Seventeen beta-estradiol, which affects cells of neural crest origin, has been shown to increase activity of the enzyme tyrosinase when added to melanocyte cultures.[3] Tyrosinase oxidizes 3, 4-dihydroxyphenylalanine (DOPA) to dopaquinone, leading to the formation of melanin.[4] Due to its importance in the formation of melanin, tyrosinase is often the target of depigmentation therapies.

Genetic predisposition, the aforementioned oral contraceptives, hormone replacement therapy, progesterone, and certain medications have also been implicated in triggering melasma. This author believes that heat exposure may play a contributing role as well (similar to that of erythema *ab igne*, a reticulated erythematous hyperpigmented eruption caused by chronic heat exposure), because melasma of the upper lip is frequently reported in women who have had hot wax applied to the area for hair removal, although no studies have documented this.[5]

"Because melasma affects women of color more frequently than Caucasian women, physicians should be aware of cultural, psychosocial, and possibly economic factors that may affect patient behavior and compliance."

Cultural Issues May Impede Compliance

Because melasma affects women of color more frequently than Caucasian women, physicians should be aware of cultural, psychosocial, and possibly economic factors that may affect patient behavior and compliance. In women of color, in which wrinkles and other signs of photoaging are less evident, dark pigmentations may be particularly distressing because they are viewed as a sign of aging.[6] Due to the protection afforded by melanin, darker-skinned individuals are at lower risk for skin cancer and sunburn. They may therefore be less likely to

Figure. Efficacy of a Triple-Combination Cream for Melasma

Asian patient with skin phototype III with moderate disease before (left) and after (right) treatment for facial melasma with a novel triple-combination cream containing hydroquinone, tretinoin, and fluocinolone acetonide.

wear sunscreen, thereby precipitating or exacerbating melasma occurrence. In addition, many sunscreen formulations look unattractive on dark skin, raising compliance issues. Sunscreens containing titanium dioxide, for example, may leave a pasty white residue that is readily apparent on darker skin types. Other formulations may leave a violet hue. The newer micronized products, such as microfine titanium dioxide or zinc oxide, which contain submicroscopic particles, may be more acceptable. Tinted products also may reduce the whitening effect.

Individuals with hyperpigmentation may resort to using over-the-counter bleaching agents to self-treat. The most frequently used bleaching agent is hydroquinone, which carries a risk of causing exogenous ochronosis (presenting as blue-black macules) when used at high concentrations.[7] In the United States, where exogenous ochronosis is rare, hydroquinone is available over the counter in 2% concentrations and via prescription at 4% strength. However, stronger concentrations are available abroad.

Benefits and Limitations of Current Therapies

Good patient education is essential in treating melasma. Patients need to understand that melasma often recurs after successful treatment and they need to be vigilant about wearing sunscreen 24 hours a day, as well as practicing sun avoidance, wearing hats, and similar protective behaviors. The sunscreens need to be broad-spectrum products that block UVA as well as UVB rays with a sun protection factor (SPF) as high as the patient can tolerate (SPF 30 or higher is recommended). Patients need to understand that UVA rays can penetrate ordinary glass and they should wear sunscreen even when indoors and while driving or riding in vehicles. Physicians may want to recommend that patients put UVA-blocking shields on their home or car windows.

Treatment typically involves the application of some kind of topical depigmenting agent (**See Table**). Hydroquinone, the most common agent, works by inhibiting tyrosinase and is cytotoxic to melanocytes.[8] Other tyrosinase inhibitors that have been studied include arbutin, kojic acid, glabridin (licorice extract), and paper mulberry. Azelaic acid is a depigmenting agent that works through antiproliferative and cytotoxic effects on melanocytes. Although hydroquinone and the other agents are effective at lightening pigmented areas, a major drawback is that they require months of daily use before results are seen. It is this author's experience that hydroquinone may have tachyphylaxis issues after prolonged use and that a one-month washout period before resuming hydroquinone restores its effectiveness.

Although effective as monotherapy, depigmenting agents are often combined with other agents, such as tretinoin (itself a depigmenting agent), hydroxy acids, and low-potency steroids, to increase their effectiveness. Both tretinoin and glycolic acid (a hydroxy acid) are thought to enhance the effectiveness of hydroquinone. Low-potency steroids are added to formulations to reduce possible irritation from the other agents.

There are myriad combination products available to the physician. Perhaps the best-known combination therapy is the Kligman formula, developed in 1975. It is a mixture of 5.0% hydroquinone, 0.1% tretinoin, and 0.1% dexamethasone, a corticosteroid.[9] It is not commercially available and must be formulated by a pharmacy. Several pharmaceutical companies have attempted to improve on the formula since then, manufacturing compounds that are variations on the hydroquinone plus tretinoin plus corticosteroid concept. Earlier this year, the U.S. Food and Drug Administration approved a triple-combination formula containing 4.0% hydroquinone, 0.05% tretinoin, and 0.01% fluocinolone acetonide (a low-potency steroid), Tri-Luma Cream, to treat melasma.

Chemical peeling agents, such as glycolic acid peels and/or Jessner peels, are frequently used in combination with topical agents to treat melasma. However, they should be used with caution on darker skin types, because of the risk of postinflammatory hyperpigmentation.[10] Lasers have been used to treat other pigmentation disorders with success, but their efficacy with melasma has not been shown. Postinflammatory hyperpigmentation was noted in Asian and dark-skinned individuals after treatment.[11] Lasers should be considered a treatment of last resort for recalcitrant melasma.

In summary, melasma is a chronic hyperpigmentation disorder that affects women of color disproportionately. Standard therapy typically involves application of topical depigmenting agents as monotherapy or in combination with other agents that increase efficacy and/or reduce irritation. The key to reducing pigmentation and preventing recurrence after successful treatment is the use of broad-spectrum sunscreen during and after treatment. Other modes of therapy, such as chemical peels and lasers, should be used with caution on skin of color.

Table. Depigmenting Agents

TYROSINASE INHIBITORS	MELANOCYTE-CYTOTOXIC AGENTS
Arbutin	Azelaic acid
Glabridrin	
Hydroquinone	**OTHER AGENTS**
Kojic acid	Alpha-hydroxy, beta-hydroxy acid peels
Paper mulberry	Resorcinol peels
	Soy
	Tretinoin
	Vitamin C

Source: Baumann L. *Cosmetic Dermatology: Principles and Practice*. New York, McGraw-Hill, 2002.

References

1. Grimes PE, Stockton T. Pigmentary disorders in blacks. *Dermatol Clin*. 1988;6:271-281.
2. Mandry Pagan R, Sanchez JL. Mandibular melasma. *P R Health Sci J*. 2000;19:231.
3. McLeod SD, Ranson M, Mason RS. Effects of estrogens on human melanocytes in vitro. *J Steroid Biochem Mol Biol*. 1994;49(1):9-14.
4. Freedberg IM, Eisen AZ, Wolff K, et al. (eds.): *Fitzpatrick's Dermatology in General Medicine, 5th ed*. New York, McGraw-Hill, 1999; p. 966.
5. Baumann L. *Cosmetic Dermatology: Principles and Practice.* New York, McGraw-Hill, 2002; p. 65.
6. Halder RM. The role of retinoids in the management of cutaneous conditions in blacks. *J Am Acad Dermatol*. 1998;39:S98-S103.
7. Taylor SC. Skin of color: Biology, structure, function, and implications for dermatologic disease. *J Am Acad Dermatol*. 2002;46:S41-S62.
8. Penney KB, Smith CJ, Allen JC. Depigmenting action of hydroquinone depends on disruption of fundamental cell processes. *J Invest Dermatol*. 1984;82:308.
9. Kligman AM, Willis I. A new formula for depigmenting human skin. *Arch Dermatol*. 1975;111:40.
10. Grimes PE. Melasma: Etiologic and therapeutic considerations. *Arch Dermatol*. 1995;131(12):1453-1457.
11. Piamphongsant T. Treatment of melasma: A review with personal experience. *Int J Dermatol*. 1998;37:897-903.

Clinical Pharmacology and Safety of a Novel Triple-Combination Agent in the Treatment of Melasma

Helen Mary Torok, MD

Melasma is a pigmentary disorder that is usually triggered by hormonal activity, such as pregnancy or oral contraceptive use, and precipitated by UVB and UVA exposure. Without treatment, melasma can persist for months or years, and, to the distress of patients, often recurs after successful treatment.

Earlier this year, the U.S. Food and Drug Administration (FDA) approved a triple-combination product as the newest addition to the dermatologist's arsenal of depigmenting agents to treat melasma. This novel triple-combination cream contains 4.0% hydroquinone, 0.05% tretinoin, and 0.01% fluocinolone acetonide in a hydrophilic base.

"Investigators have known for more than two decades that a combination of hydroquinone, tretinoin, and a corticosteroid is more effective than any of the agents used alone."

Three Agents Prove Synergistic

Before examining how the three agents might work in combination, it is beneficial to examine the mechanism of action of each individually.

Hydroquinone, both as monotherapy and in combination with one or more agents, has been the treatment modality of choice for five decades for melasma and postinflammatory hyperpigmentation. It is prepared from the reduction of *p*-benzoquinone with sodium bisulfite. Hydroquinone works by inhibiting tyrosinase, the enzyme that facilitates the conversion of the amino acid tyrosine into eumelanin and pheomelanin.[1]

Tretinoin is all-*trans*-retinoic acid formed from the oxidation of the aldehyde group of retinene to a carboxyl group. Like hydroquinone, it has been used as monotherapy in the treatment of melasma. Tretinoin is thought to reduce the transfer of the melanosomes from the melanocytes to the keratinocytes.[2] It causes an increase in epidermal proliferation, which accelerates the hypopigmentation process but can cause skin irritation in some patients. Tretinoin is known to enhance the epidermal penetration of the hydroquinone. It also protects against possible atrophy from topical steroids.[3]

The third active ingredient, fluocinolone acetonide, is a synthetic fluorinated corticosteroid for topical dermatological use and is classified therapeutically as an antiinflammatory. It ameliorates the possible erythema, scaling, and irritation that are frequently associated with tretinoin use. It is a low-potency, class VI corticosteroid and should not be confused with the high-potency, class II corticosteroid fluocinonide. Fluocinolone acetonide has a proven safety record and has been approved by the FDA for application anywhere on the body for atopic dermatitis in pediatric patients.

Investigators have known for more than two decades that a combination of hydroquinone, tretinoin, and a corticosteroid is more effective than any of the agents used alone.[2] The novel triple combination described here was tested in two clinical trials against creams containing two of the three active ingredients and was shown to be significantly more effective than any of the dyads.[4]

In addition to the synergistic effect apparent from the triple-combination cream, another benefit is simplified usage, which encourages patient compliance. The relatively quick results (typically 4 weeks or less, compared to 16 to 20 weeks for hydroquinone monotherapy and possibly longer for tretinoin monotherapy) also encourage compliance, as does the improvement patients see from using a retinoid product. Retinoid effects of smoothing, diminished pore size, and photorejuvenation are evident. Patients see this overall rejuvenation of the skin as a bonus to the lightening of the melasma.

Figure 1. Triple-Combination Cream Tested Against Three Dyads

The triple-combination cream was found to be significantly more effective at treating melasma than three creams containing two of the three active ingredients. Asian patient, shown before (left) and after (right) treatment with the triple-combination cream, has skin type III with severe disease.

Combination Cream Tested in 8-Week, 12-Month Studies

Pharmacokinetics studies on 59 volunteers found minimal percutaneous absorption of the three active ingredients following 8 weeks' daily application of the triple-combination cream. It should be noted that although the cream contains sodium metabisulfite, no systemic reactions from sulfite-sensitive individuals have been observed in safety data compiled on more than 1,000 patients to date.[5] Systemic absorption of topical corticosteroids can produce reversible hypothalamic-pituitary-adrenal (HPA) axis suppression; however, given the small amount of body surface area affected, the relatively brief duration of therapy, and the fact that no occlusion is indicated, this is not likely to be an issue of concern. There was no HPA suppression in the pediatric patients who used fluocinolone acetonide for atopic dermatitis.

Efficacy results of the combined clinical trials that tested the triple-combination cream against three creams that contained two of the three active ingredients are presented elsewhere in this supplement. Adverse events—primarily erythema, desquamation, burning, dryness, and pruritus—were deemed mild for all four study arms. The highest percentage of adverse events was experienced by the group who received the hydroquinone and tretinoin cream—80% experienced at least one adverse event. Sixty-five percent of the subjects on the tretinoin plus fluocinolone cream had at least one adverse event. For the triple-combination cream, it was 63%. For the fluocinolone plus hydroquinone dyad, 35% had at least one adverse event.[6]

Among 161 subjects in the 8-week study who used the triple-combination cream, 41% experienced erythema, 38% desquamation, 18% burning, 14% dryness, and 11% pruritus. In a 12-month long-term safety study, a significant number of patients had cumulative treatment with the triple-combination cream totaling 6 months and showed a similar pattern of adverse events as in the 8-week study.[7]

"Patient education regarding use of broad-spectrum sunscreen and sun avoidance both during and after treatment to minimize risk of recurrence cannot be emphasized enough."

Battling Recurrence

One of the factors that makes melasma so therapeutically challenging is its high incidence of recurrence. Patient education regarding use of broad-spectrum sunscreen and sun avoidance both during and after treatment to minimize risk of recurrence cannot be emphasized enough. The patient is encouraged to switch to nonhormonal forms of birth control if she is currently using hormonal methods. The triple-combination cream discussed here is approved for short-term treatment of facial melasma, not as maintenance therapy. One approach is for physicians to use it as a "jump-start" treatment for 2 months in which patients can see fast results. Once the melasma is cleared, other bleaching products can be used as maintenance therapy. The triple-combination cream discussed here is approved for short-term treatment of moderate to severe facial melasma, not as maintenance therapy. However, therapy may be restarted if melasma recurs.

Figure 2. Efficacy of a Triple-Combination Cream for Melasma

The triple-combination cream was tested in two 8-week clinical trials. Study participants had skin phototypes I-IV and melasma ranging from moderate to severe. Patient, shown before (left) and after (right) treatment with the triple-combination cream, exhibits a Caucasian skin type II with moderate disease.

References

1. Penney KB, Smith CJ, Allen JC. Depigmenting action of hydroquinone depends on disruption of fundamental cell processes. *J Invest Dermatol*. 1984;82:308.
2. Kligman AM, Willis I. A new formula for depigmenting human skin. *Arch Dermatol*. 1975;111:40.
3. McMichael AJ, Griffiths CE, Talwar HS, Finkel LJ, Rafal ES, et al. Concurrent application of tretinoin (retinoic acid) partially protects against corticosteroid-induced epidermal atrophy. *Br J Dermatol*. 1996;135(1):60-64.
4. Taylor SC, Torok H, Jones T, Lowe N. Efficacy and safety of a new triple combination agent for the treatment of facial melasma. Poster presented at the annual meeting of the American Academy of Dermatology; New Orleans, LA; February 22-27, 2002.
5. Data on file, Galderma Laboratories, L.P., Fort Worth, Texas.
6. Data on file, Galderma Laboratories, L.P., Fort Worth, Texas.
7. Data on file, Galderma Laboratories, L.P., Fort Worth, Texas.

Efficacy of a Novel Triple-Combination Agent in the Treatment of Facial Melasma

Susan C. Taylor, MD

Although numerous depigmenting agents exist to treat facial melasma, their use has various limitations—including many months of therapy, erythema, burning, and desquamation of the application site, and a lack of efficacy. These limitations have led to the continued search for novel combination therapies that are more efficacious, faster to bring results, and have fewer adverse reactions.

It has been more than a quarter-century since Kligman and Willis published their paper demonstrating that a cream combining hydroquinone, tretinoin, and a corticosteroid had synergistic action in depigmenting skin.[1] A new formula, designed to eliminate or minimize adverse events and to simplify usage, has been developed that is a refinement of the classic Kligman formula (which is unavailable commercially and must be prepared by a pharmacist). The new topical cream contains 4.0% hydroquinone (HQ), 0.05% tretinoin (RA), and 0.01% fluocinolone acetonide (FA), a low-potency corticosteroid, in a hydrophilic base.

"These limitations [in current therapies] have led to the continued search for novel combination therapies that are more efficacious, faster to bring results, and have fewer adverse reactions."

Triple-Agent Cream Pitted Against Three Dyads

This triple-combination formula was tested in two multi-center, randomized, double-blind phase III trials.[2] The two 8-week studies comprised 13 centers and a total of 641 subjects, 98% female, between 21 and 75 years of age. The study participants had skin phototypes I through IV and moderate to severe melasma of the face. (A Melasma Severity Rating Scale of 0–3 was used and the rating was based on the investigator's assessment. A score of 2, moderate melasma, was defined as moderately darker than the surrounding normal skin, and a score of 3, severe melasma, was defined as markedly darker than the surrounding skin.)

All subjects were randomized to receive either the triple-combination cream (HQ + RA + FA) or one of three dyads containing two of the three active ingredients (RA + FA, HQ + FA, and RA + HQ). The dyad formulations used the same hydrophilic base as the triple-combination cream.

The subjects were evaluated for melasma severity at baseline and reevaluated at 1, 2, 4, and 8 weeks. The studies, whose combined results are presented here, had two efficacy end points. The primary end point was the proportion of intent-to-treat subjects in each group who achieved complete clearing at week 8 (melasma severity score of 0, defined as melasma lesions approximately equivalent to surrounding normal skin). The secondary end point was the proportion of intent-to-treat subjects who achieved complete or near-complete clearing (melasma severity score of 0 or 1; a score of 1, mild melasma, was defined as slightly darker than the surrounding skin).

The subjects were instructed to apply the study medication once daily at bedtime, after cleansing their face with a mild soapless cleanser. They were told to apply a thin layer of the cream to the pigmented lesion and the outside borders. Subjects were given a moisturizer to use if they experienced dryness, as well as an SPF 30 sunscreen to apply daily. They were also counseled on sun avoidance and to wear protective clothing when outdoors.

Figure. Melasma Disproportionately Affects Women of Color

Patient, shown before (left) and after (right) treatment with the triple-combination cream, has skin type IV with moderate disease and is one-half African American, one-half Caucasian.

More Combination Cream Subjects Achieve Complete Clearing

At the end of the 8 weeks, more subjects treated with the HQ + RA + FA cream achieved complete clearing (29%) compared to each of the dyads: 2% of the RA + FA group, 3% of the HQ + FA group, and 10% of the RA + HQ group experienced complete clearing.

For the secondary efficacy end point—proportion of intent-to-treat subjects who experienced complete or near-complete clearing—77% of the subjects treated with the HQ + RA + FA

Table. Investigators' Assessment of Change in Melasma Severity From Baseline to Day 56 of Treatment (combined results from studies 1 and 2)

	BASELINE		NUMBER (%) OF PATIENTS AT DAY 56[a]				
			CLEARED[b]	MILD[b]	MODERATE[b]	SEVERE[b]	MISSING[b]
	Severity Rating	N	N (%)	N (%)	N (%)	N (%)	N (%)
Triple-combination agent[c]	Moderate	124	36 (29)	63 (51)	18 (15)	0 (0)	7 (6)
N=161	Severe	37	6 (16)	19 (51)	9 (24)	2 (5)	1 (3)

[a] Assessment based on patients with severity scores at Day 56. Percentages are based on the total number in the treatment group population.
[b] Does not include patients who cleared before Day 56 or were missing from the Day 56 assessment. Assessment Scale: Cleared (melasma lesions approximately equivalent to surrounding normal skin or with minimal residual hyperpigmentation); Mild (slightly darker than the surrounding normal skin); Moderate (moderately darker than the surrounding normal skin); Severe (markedly darker than the surrounding normal skin).
[c] 4.0% hydroquinone, 0.05% tretinoin, 0.01% fluocinolone acetonide.

Source: Data on file, Galderma Laboratories, L.P., Fort Worth, Texas, 2002.

cream attained this level of improvement, much more than in any of the dual-therapy groups (27% of the RA + FA group, 42% of HQ + FA group, and 47% of the RA + HQ group). Again, this difference between the triple combination cream and each of the dual therapies was statistically significant. Another way to frame the results is that three-fourths of the subjects treated with the triple-combination cream went from a melasma severity score of 2 or 3 to a score of 0 or 1. It should be noted that subjects who went from moderate or severe melasma to mild melasma viewed this as a marked improvement.

Let us look more closely at the study arm involving the 161 subjects who received the triple-combination cream: The 124 subjects who had moderate melasma at baseline when evaluated at 8 weeks showed 29% rated cleared, 51% rated mild, 15% rated moderate, and none rated severe, with 6% not completing the study. Of the 37 subjects rated severe at baseline, 16% were rated cleared, 51% were rated mild, 24% were rated moderate, 5% were still rated severe, and 3% were missing at the conclusion. Subjects typically experienced improvement of their melasma with the triple-combination cream as early as 4 weeks.

Of the adverse events reported, the most frequently occurring reactions in the HQ + RA + FA cream group were application site erythema, desquamation, burning, dryness, and pruritus. However, none of the subjects receiving the triple-combination cream discontinued the study due to adverse events. The majority of adverse events in all four treatment arms were deemed mild in severity. Importantly, with the triple-combination therapy there was no incidence of dermal atrophy, which has been a concern in the past when using corticosteroids on the face.

"...with the triple-combination therapy there was no incidence of dermal atrophy, which has been a concern in the past when using corticosteroids on the face."

Conclusion

In summary, the HQ + RA + FA cream was numerically as well as statistically significantly more effective at treating melasma than three creams containing two of the three active ingredients. This triple-combination formulation poses no additional risks compared to its individual drug components. It is safe and effective in daily applications for short-term treatment of melasma of the face.

References

1. Kligman AM, Willis I. A new formula for depigmenting human skin. *Arch Dermatol*. 1975;111:40.
2. Taylor SC, Torok H, Jones T, Lowe N. Efficacy and safety of a new triple combination agent for the treatment of facial melasma. Poster presented at the annual meeting of the American Academy of Dermatology; New Orleans, LA; February 22-27, 2002.