Azelaic acid modulates the inflammatory response in normal human keratinocytes through PPARgamma activation.

Mastrofrancesco A, Ottaviani M, Aspite N, Cardinali G, Izzo E, Graupe K, Zouboulis CC, Camera E, Picardo M.

Laboratorio di Fisiopatologia Cutanea e Centro Integrato di Metabolomica, San Gallicano Dermatologic Institute IRCCS, Rome, Italy.

Abstract

Azelaic acid (AzA), a nine-carbon dicarboxylic acid, is an agent for the topical treatment of acne. It has also been shown to be effective in rosacea; however, the mechanism of action has not been clarified. Because inflammation is a common feature of both conditions, we investigated the effects of azelaic acid on the inflammatory response of normal human keratinocytes to ultraviolet B light, which is a photosensitizer agent in rosacea. AzA, at 20 mM, a concentration achievable following topical application of a 15% gel, suppresses ultraviolet B light-induced interleukins-1beta, -6 and tumor necrosis factor-alpha mRNA expression and protein secretion. Mechanistically, azelaic acid significantly reduced the ultraviolet B light-induced nuclear translocation of nuclear factor kB p65 subunit and the phosphorylation of the p38 mitogen and stress-activated protein kinase. Moreover, as peroxisome proliferators-activated receptor gamma, (PPARgamma) which has a crucial role in the control of inflammation, is activated by fatty acids and products of lipid peroxidation, we further investigated the effect of azelaic acid on the expression of this nuclear receptor. AzA induced peroxisome proliferators-activated receptor-gamma mRNA and its transcriptional activity. The PPARgamma antagonist GW9662 abrogated the inhibitory effects of AzA on the UVB-induced pro-inflammatory cytokines release and on the cell proliferation. Our study provides new insights into the molecular mechanisms of the activity of azelaic acid and lands additional evidences for its therapeutic effects on inflammatory skin diseases, such as rosacea.

PMID: 20545756 [PubMed - indexed for MEDLINE]
Skin lightening preparations and the hydroquinone controversy.

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Abstract

Skin lightening preparations are widely used in dermatology by persons of all Fitzpatrick skin types. Fitzpatrick skin types I-III require local pigment lightening for the treatment of hormonally induced melasma and postinflammatory hyperpigmentation caused by acne and trauma. Fitzpatrick skin types IV and darker have an even greater need for skin lightening for social reasons, as well as pigmentary changes that occur around the eyes, in the intertriginous areas, following dermatitis, or with acne and trauma. The gold standard dermatologic agent for skin lightening was hydroquinone, until regulatory agencies in Japan, Europe, and most recently in the United States questioned the safety of this substance. This has encouraged research into alternative agents to inhibit skin pigmentation such as retinoids, mequinol, azelaic acid, arbutin, kojic acid, aleosin, licorice extract, ascorbic acid, soy proteins, and N-acetyl glucosamine. The efficacy and safety of each of these ingredients is examined as possible topical alternatives to hydroquinone.

PMID: 18045355 [PubMed - indexed for MEDLINE]
The use of topical azelaic acid for common skin disorders other than inflammatory rosacea.

Del Rosso JQ.

University of Nevada School of Medicine, Las Vegas, USA.

Abstract

Topical azelaic acid (AzA) is approved for the treatment of acne vulgaris and inflammatory (papulopustular) rosacea. Because of diverse mechanisms of action that correlate with potential therapeutic benefit, AzA has been used to treat several common dermatoses including acne vulgaris, inflammatory rosacea, erythematotelangiectatic rosacea, perioral dermatitis, melasma, and postinflammatory hyperpigmentation. This article reviews the therapeutic use of topical AzA for the treatment of common skin disorders other than the US Food and Drug Administration (FDA)-approved indications of acne vulgaris and inflammatory rosacea.

PMID: 16566285 [PubMed - indexed for MEDLINE]

Rosacea, reactive oxygen species, and azelaic Acid.

Jones DA.

Department of Dermatology, Brigham and Women's Hospital, Boston, Massachusetts.

Abstract

Rosacea is a common skin condition thought to be primarily an inflammatory disorder. Neutrophils, in particular, have been implicated in the inflammation associated with rosacea and mediate many of their effects through the release of reactive oxygen species. Recently, the role of reactive oxygen species in the pathophysiology of rosacea has been recognized. Many effective agents for rosacea, including topical azelaic acid and topical metronidazole, have anti-inflammatory properties. in-vitro models have demonstrated the potent antioxidant effects of azelaic acid, providing a potential mechanistic explanation for its efficacy in the treatment of rosacea.
Photoprotective effects of nicotinamide.

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Abstract

Sun protective measures can reduce numbers of both precancerous actinic keratoses and cutaneous squamous cell carcinomas within relatively short periods of time even in high-risk populations. Sunscreens, which tend to provide greater protection against shortwave UVB than against longer wavelength UVA radiation, can however provide only partial protection from the mutagenic and immune suppressive effects of sunlight. In large part, this reflects poor compliance with proper sunscreen application and reapplication. Skin cancer is by far the most common malignancy in Caucasian populations, and additional strategies to reduce the morbidity and economic burden of this disease are now urgently needed. Nicotinamide, the amide form of vitamin B3, is an inexpensive agent which is used for a variety of dermatological applications with little or no toxicity even at high doses. *Nicotinamide has photoprotective effects against carcinogenesis and immune suppression in mice, and is photoimmunoprotective in humans when used as a lotion or orally*. UV irradiation depletes keratinocytes of cellular energy and nicotinamide, which is a precursor of nicotinamide adenine dinucleotide, may act at least in part by providing energy repletion to irradiated cells.

PMID: 20354654 [PubMed - indexed for MEDLINE]
Visualization of the melanosome transfer-inhibition in a mouse epidermal cell co-culture model.


Department of Biological Engineering, National Research Laboratory of Skin-bioactive Material, Inha University, Incheon 402-751, Korea.

Abstract

Transfer of melanin-containing melanosomes from melanocytes to neighboring keratinocytes results in skin pigmentation. To provide a more practical method of visualizing melanosomes in melanocytes as well as in keratinocytes, we attempted to use murine cell lines instead of human primary cells. We generated various fluorescent fusion proteins of tyrosinase, a melanin synthesis enzyme located in the melanosome, by using green fluorescent protein and red fluorescent protein. The intracellular localization of tyrosinase was then examined by fluorescence and confocal microscopy. Co-culture of murine melanocytes and keratinocytes was optimized and melanosome transfer was either stimulated with alphaMSH or partially inhibited by niacinamide. To the best of our knowledge, this is the first study showing that a murine co-culture model, in addition to human primary cell co-culture, can be a good tool for depigmenting agent screening by monitoring melanosome transfer.

PMID: 20043134 [PubMed - indexed for MEDLINE]

The treatment of melasma. 20% azelaic acid versus 4% hydroquinone cream.

Baliña LM, Graupe K.

Source

Department of Dermatology, Argerich Hospital, Buenos Aires, Argentina.

Abstract

The efficacy of 20% azelaic acid cream and 4% hydroquinone cream, both used in conjunction with a broad-spectrum sunscreen, against melasma was investigated in a 24-week, double-blind study with 329 women. Over the treatment period the azelaic acid cream yielded 65% good or excellent results; no significant treatment differences were observed with regard to overall rating, reduction in lesion size, and pigmentary intensity. Severe side effects such as allergic sensitization or exogenous ochronosis were not observed with azelaic acid.

PMID: 1816137 [PubMed - indexed for MEDLINE]
Evidence-based topical skin rejuvenation

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¹ Department of Dermatology, University Hospital of Zurich, Zurich, Switzerland

*these authors have contributed equally to this study

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Introduction:
A large choice of agents with preventive or rejuvenating effects is available. However, which ones should be chosen and recommended to our patients? The published clinical studies on the effect of topical agents in the reduction of facial wrinkles in vivo lack accepted measuring standards and defined endpoints.

As a clinical indicator of efficacy, we noted the maximal clinical effect on facial wrinkles of each compound, together with the duration and type of each study. In addition, we compared the extent of epidermal thickening that the different agents were able to elicit.

Epidermal thickness increase by compounds used to treat wrinkles

<table>
<thead>
<tr>
<th>Compound/ Formulation</th>
<th>Max. increase epidermal thickness</th>
<th>Study design</th>
<th>Duration of trial</th>
<th>Compared to</th>
<th>Study by</th>
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<tbody>
<tr>
<td>Tretinoin 0.05%</td>
<td>24 wks</td>
<td>6.6%</td>
<td>v, 36-44 yrs</td>
<td>placebo</td>
<td>2001</td>
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<tr>
<td>Lactic acid 8%</td>
<td>12 wks</td>
<td>5.3%</td>
<td>v, 36-44 yrs</td>
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<td>2001</td>
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<td>Niacinamide 4%</td>
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<td>v, 26-32 yrs</td>
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<td>v, 25-35 yrs</td>
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<td>2001</td>
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<td>Pal-KTTKS</td>
<td>24 wks</td>
<td>26%</td>
<td>v, 50-60 yrs</td>
<td>placebo</td>
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<td>Aloe vera</td>
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<td>v, 50-60 yrs</td>
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<td>2001</td>
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<td>Topical estrogens</td>
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<td>v, 25-35 yrs</td>
<td>placebo</td>
<td>2001</td>
</tr>
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<td>29%</td>
<td>v, 25-35 yrs</td>
<td>placebo</td>
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<td>33%</td>
<td>v, 25-35 yrs</td>
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<td>Green tea</td>
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<td>24 wks</td>
<td>v, 50-60 yrs</td>
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Methods:
We performed a literature search in Pubmed among clinical trials with the keywords “skin” and “wrinkle” or “aging” or “antiaging”. The search was done within articles published in between 01.01.1999 and 01.06.2009; older articles were included if they were mentioned as precedent in newer articles and the methodology and results of the study were found to be appropriate and reliable. The search yielded 476 articles. We manually looked for clinical trials within the resulting list. The shaded lines in the tables indicate that no statistical relevance was reached or no relevant statistics were published.

Conclusion:
Tretinoin reduced facial wrinkles (-20 to -50%) and induced epidermal thickening (+24 to +44.5%). Niacinamide (-34 to -52%) and lipic acid (-51%) showed similar efficacy on facial wrinkles, while estrogens were less effective (-21% on facial wrinkles) but induced epidermal thickening (+75%). The phytoestrogen genistein induced weaker epidermal thickening (+20%) without showing convincing effects on wrinkles. Vitamin C had an intermediate effect on wrinkles (-34% to -29%).

The collagen-inducing tripeptide pal-KTTKS (-18% wrinkles, no significant difference to placebo), ectoin (-23%) and kinetin (-13%), and green tea extracts had no effect at all.

Taken together, a simple global analysis of efficacy shows differences between the agents already today, although higher quality randomized placebo controlled double blind studies, accepted measuring standards and defined objective endpoints are needed for the future.
New Insights Into Azelaic Acid

As we learn more about this agent, we also discover new ways of understanding and approaching rosacea, acne, and hyperpigmentation.

BY JOSHUA ZEICHNER, MD

This month marks the 10th year since azelaic acid has been commercially available under the brand name of Finacea Gel (Bayer). Indicated for mild to moderate papulopustular rosacea, Finacea was FDA approved in December 2002, and released in March 2003. Over the past decade, research has elucidated the pathways through which it works, and several new applications have been reported in the literature. The following will review recent advances, the latest data, and uses for this unique agent.

BACKGROUND

Azelaic acid is a naturally occurring dicarboxylic acid derived from rye, wheat, and barley. A single mechanism of action has not been identified to explain the effects of azelaic acid on the skin. It helps scavenge reactive oxygen species, reduces expression of kallikrein-5 (KLK-5) and pro-inflammatory cathelicidins such as LL-37, as well as inhibits toll-like receptor 2 (TLR-2). In addition, it inhibits the pigment producing enzyme tyrosinase, has comedolytic properties, and may reduce epidermal hyperkeratinization.

AZELAIC ACID FOR ROSACEA

The 15% gel formulation of azelaic acid is FDA approved to treat the papules and pustules of mild to moderate rosacea. While the 15% gel has a lower concentration of azelaic acid compared to the 20% cream, advances in formulation technology give the gel greater cutaneous bioavailability. While the indication is for use of azelaic acid 15% gel twice daily, a study subsequent to its approval demonstrated equivalent efficacy of once compared to twice daily application.

Recent data suggest abnormal over-activity of the innate immune system as a major contributor to the pathophysiology of rosacea. Excess skin antimicrobial peptides (e.g., cathelicidins) and stimulation of TLR-2 both play significant roles. Cathelicidins are processed by serine proteases (e.g., KLK-5) into pro-inflammatory peptides, such as LL-37. Overactivity of KLK-5 leads to a high level of cathelicidin processing into peptides with greater pro-inflammatory properties than antibacterial properties. This imbalance promotes angiogenesis and chronic skin inflammation. Topical application of azelaic acid 15% gel has been demonstrated to reduce skin serine protease activity and help reverse these changes.

AZELAIC ACID FOR ACNE

TLR-2 over-activity plays a role in the pathogenesis of acne. Propionibacterium acnes itself has been shown to stimulate TLR-2 activity, resulting in skin inflammation and comedogenesis. Topical retinoids are a staple in treating acne not only because of their ability to normalize follicular hyperkeratinization but also due to their anti-inflammatory properties. Similar to its mechanism of action in treating rosacea, azelaic acid’s ability to inhibit TLR-2 activity helps explain its efficacy in treating acne vulgaris. The use of azelaic acid 15% gel is considered off label for the treatment of acne vulgaris. Many practitioners may use it off-label for acne as part of a combination therapy for patients who cannot tolerate topical retinoids, those who also suffer from hyperpigmentation, and for women who are pregnant or breastfeeding (as it is pregnancy category B).

AZELAIC ACID FOR HYPERPIGMENTATION

Post-inflammatory pigmentation clinically manifests as dark spots in areas of skin that previously were inflamed, be it from acne or another inflammatory dermatosis. While not
improved for this indication, azelaic acid is commonly used off-label to treat pigmentation. One clinical trial demonstrated 15% azelaic acid gel to be both efficacious and safe in treating hyperpigmentation associated with acne for 16 weeks. This effect may be explained by two properties of the drug. First, azelaic acid is known to inhibit the enzyme tyrosinase, which is needed for the production of melanin. Second, its role as an anti-inflammatory may be beneficial as well. When active acne lesions (e.g., papules and pustules) resolve, evidence shows that the skin in these areas still possess subclinical inflammation. While this has been demonstrated in acne scars, the same may also be true in cases of persistent erythema and pigmentation. More research is needed to substantiate this theory, however.

CONCLUSION

Having a drug that effectively treats a condition helps us better understand that condition, as we discover the mechanism by which the drug works. Just as biologics have shed light on the pathogenesis of psoriasis, research into the mechanism of action of azelaic acid has greatly improved our knowledge about the pathogenesis of rosacea, specifically the role of an over-active innate immune system. A greater understanding of the disease translates to improved treatment algorithms and patient outcomes, and ultimately this helps influence the future of drug development.

Dr. Zeichner has served as a consultant for Allergan and Bayer.

Joshua Zeichner, MD, FAAD is an Assistant Professor and Director of Cosmetic and Clinical Research in the Department of Dermatology at Mount Sinai Medical Center in New York.

Taking the Pulse of Hydroquinone Therapy: A Plea for Caution

Pulse therapy under physician supervision can reduce long-term exposure and help reduce the risk of untoward effects of hydroquinone therapy.

BY ZEIN E. OBAGI, MD

For many consumers, hydroquinone is like an old friend who inexplicably turns on you. They may have used it for years, trusting that their dermatologist—or, frequently, some Internet pharmacy—would never recommend a product that could harm them.

But over time, some of these consumers develop new pigment problems in the areas where they have faithfully applied hydroquinone. The product they bought to lighten sunspots, melasma, or other hyperpigmentation paradoxically leaves them with tough-to-treat issues such as severe rebound hyperpigmentation and ochronosis.

Avoiding such side effects requires a shift in our approach to hydroquinone. Specifically, my research and clinical experience have convinced me that our patients should use hydroquinone for no more than four or five months at a time. Then we must give the skin a break and allow it to stabilize before deciding if another course of hydroquinone is warranted. I call this approach Pulsed Hydroquinone Therapy.

MEDICAL PRODUCTS NEED MEDICAL SUPERVISION

I have always been a strong proponent of hydroquinone. Used in reasonable concentrations, under physician supervision, it is safe and effective for pigment problems ranging from chloasma, melasma and postinflammatory hyperpigmentation (PIH) and to prepare skin for treatment of less common concerns such as nevi of Ota and Huri which require pigment laser.

But over the last several years, the Internet has become inundated with discounted, medical-grade products that companies sell directly to consumers without proper medical supervision or sun protection.

Consumers want to save themselves a consultation fee or doctor visit. I see no problem with buying a simple moisturizer or broad-spectrum sunscreen online. But to continue treatment with hydroquinone (or other medical-grade skin formulations, for that matter) indefinitely, without the oversight and expertise of the dermatologist who originally prescribed it, often creates dermatologic disasters.

Following are the patterns I see increasingly in my clinical practice, and the reasons behind them.

Resistance. Some people who have been using hydroquinone in proper concentration of 4% (alone or in compounded formulations) find that their skin improves for a few months, and then the improvement stops. In my experience, this is particularly common after four to five months of satisfactory response in patients using hydroquinone for melasma.

In such cases, the bleaching effects of hydroquinone appear more pronounced in the areas not affected by melasma. Meanwhile, the dark spots of melasma show no further improvement. In fact, as the active melanocytes in the affected areas develop resistance to hydroquinone, the patient’s hyperpigmentation in these areas worsens.

“Adopting the pulsed approach will spare our patients from the disfiguring and needless side effects of extended, self-directed use of hydroquinone.”
That is what happened to a 58-year-old female patient from India who was diagnosed with melasma at our clinic in 2001 (see above, Patient 1). At that time, she was treated successfully with hydroquinone 4%, and hydroquinone mixed with retinoic acid, followed by a chemical peel to the papillary dermis. A decade later, after having obtained branded hydroquinone 4% and retinoic acid products from the web and the black market, she returned and was diagnosed with rebound severe melasma (epidermal and dermal) that did not respond but worsened by her continuous hydroquinone use.

To avoid such problems, I recommend that after no more than five months of hydroquinone application, all patients should cease using this drug for two to three months. This allows melanocytes to stabilize (so they can withstand external and internal factors that might otherwise increase their activity) and restore the skin’s natural melanin. During this phase, patients can use other lightening agents, then resume hydroquinone if necessary afterward.

Some dermatologists may choose to treat resistant melasma by increasing the hydroquinone concentration. Instead, I have found that patients respond well to aggressive application of hydroquinone (4%) plus retinoic acid, combined in equal parts. This combination tends not to bleach the skin, but to accelerate attainment of a more natural and even color tone. Once the skin’s color has evened out after up to five months of treatment, I have my patients discontinue use of this mixture and switch to retinoic acid alone for two to three months; then patients resume hydroquinone application if needed.

Photosensitivity, phototoxicty. We know that certain topical agents, such as retinoids, amniroleulic acid, and some systemic medications (such as tobramycin/TCN and hydrochlorothiazide), can increase skin sensitivity to sun exposure. Surprisingly, no one, to my knowledge, has ever considered hydroquinone to be a photosensitizer.

Some patients use hydroquinone indefinitely, thinking it will prevent unwanted pigmentation. But we now know that decreasing the amount of melanin in skin, as hydroquinone does, creates photosensitivity. Without proper sunscreen use (sun protection factor/SPF ≥ 30, frequent reapplication), photosensitivity leads to inflammation, which stimulates melanin production.

The sun can also affect the melanocytes directly, increasing melanin production and possibly leading to rebound pigmentation. Furthermore, phototoxic reactions can trigger a chemically altered bluish melanin compound that’s responsible for ochronosis, which is tough to treat because it involves deep pigmentary changes deep in the dermis associated with altered skin texture.

Physicians used to consider ochronosis as a condition that was limited to certain African tribes, and we believed that it stemmed perhaps partially from genetic causes, partially from prolonged hydroquinone use.

However, in the last few years, I have observed a higher incidence of ochronosis not only in African-Americans, but also in Caucasian, Asian, and Hispanic patients who have used various concentrations of hydroquinone, often for years on end. In these patients, ochronosis has occurred in the areas of the face that experience the most sun exposure.

One such patient I saw was a 39-year-old Caucasian female. She had a history of melasma, and underwent the following treatments, prescribed by various dermatologists, in the two years prior to presenting at our clinic with severe ochronosis: three peels consisting of azelaic acid, kojic acid, phytic acid, ascorbic acid, arbutin, and titanium dioxide (Cosmelan, Mesoestetic) in one year; eight intense pulsed light (IPL) treatments; three fractional laser resurfacing (Fraxel, Solta) sessions; six Jessner’s peels; and continuous use of hydroquinone 8% throughout the two years.
This case also serves as a reminder that when treating hyperpigmentation, we should not use exfoliative procedures, chemical peels, laser resurfacing, or other thermal rejuvenating devices as our first step. Rather, I recommend proper skin conditioning—using hydroquinone, hydroquinone plus retinoic acid, alpha hydroxy acids, antioxidants, and any disease-specific agents necessary—for four to six weeks before and after any procedure (once skin healing is complete). This helps to restore normalcy and functionality to the skin, and it improves the results from procedures.

**Excessive HQ concentration.** I am used to prescribing hydroquinone concentrations of 4%, and I have treated many patients who used high concentrations on their own or under the supervision of other physicians. Based on my observations and experience, such concentrations deliver no greater or faster results than hydroquinone 4%. On the contrary, concentrations of 6-12% tend to cause more recalcitrant hyperpigmentation, quicker resistance, and a higher rate of ochronosis.

Excessive hydroquinone concentrations may induce toxic or shocking effects on melanocytes, forcing them to regroup and increase their melanin production (resulting in rebound hyperpigmentation). Additionally, high concentrations of hydroquinone may provoke skin inflammation. Used on its own, hydroquinone is an inflammatory agent that can cause redness, itching, and allergic reactions. Inflammation leads to melanocyte hyperactivity, which overpowers hydroquinone’s ability to suppress tyrosinase, leading to the rebound hyperpigmentation.

Such was the case with a 66-year-old African-American female with history of melasma who was treated for seven years by other dermatologists (Patient 2). She used hydroquinone 8%, tretinoin (Retin-A, Valeant Dermatology), and desonide cream (Desowen, Galderma) for years. Dissatisfied with the results, she eventually was prescribed hydroquinone 12%, and her dermatologist added topical steroids to her regimen. Ultimately, her worsening condition prompted this dermatologist to refer her to our office, where she was diagnosed with rebound dermal and epidermal hyperpigmentation, ochronosis with severe irritation and sensitiv-

**Hydroquinone combination formulations.** In this regard, consumers can readily find products that combine hydroquinone with various ingredients such as retinoic acid, glycolic acid, vitamin C, and topical steroids. However, prolonged use of such products can worsen pigmentation and create additional issues. This is especially true of products that combine hydroquinone, retinoic acid, and steroids e.g., Kligman’s formula and the combination of hydroquinone, tretinoin, and fluocinolone acetonide (Triluma, Galderma). I have found that long-term use of such products can lead to skin atrophy, the appearance of telangiectasias, skin sensitivity, and, frequently, more stubborn pigmentation than the patient originally had.

The topical steroids in these formulations aim to suppress inflammation. This is critical because inflammation excites melanocytes, which stimulate melanin production. However, topical steroids only work on pigmentation induced by trauma or disease (PIH). In contrast, we must avoid prescribing topical steroids for patients with pigment problems not caused by inflammation, such as melasma.

Moreover, to avoid disrupting cellular function, these triple-combination products should not be used for longer than five to seven days, in accordance with their instructions. As an alternative, I prefer the combination of hydroquinone and retinoic acid without a steroid. It is safer, yet quite effective when used properly for three to five months with strict sun protection.
RETINOIDS REQUIRE CAUTION
As with hydroquinone, however, many medical-grade ingredients, such as retinoic acid and other retinoids, if used indefinitely, may cause continuous irritation. This irritation can lead to inflammation and create more damage as the skin builds resistance to the treatment.

The following patients’ experiences are typical in this regard.

Patient 3 (photo previous page), a 59-year-old Hispanic female with a history of melasma, acne, and scarring, was successfully treated in 1990 with topical creams, isotretinoin, and trichloroacetic acid peels. Her maintenance program included hydroquinone 4% and a hydroquinone-retinoic acid combination, as described above. About five years ago, she returned to the clinic with ochronosis, primarily on the left side of her face (because she drives long distances). She is currently being treated for her ochronosis.

Patient 4 (photo previous page) is a 57-year-old African-American female, seen 25 years ago for PIH and melasma. She responded well to a topical medication that included hydroquinone 4%, used daily, and hydroquinone mixed with retinoic acid in the evening. She also had a trichloroacetic acid peel down to the papillary dermis. Subsequently, she did not follow-up with her treatments, but eventually returned many years later. She had been using the hydroquinone medications continuously, and presented with ochronosis. I had her immediately stop the hydroquinone treatment; she did not desire to treat the ochronosis, saying it did not bother her.

Based on such cases, I now view retinoic acid as a tool for general skin repair; beyond that, it is not always an ideal agent. Patients generally find retinoic acid hard to tolerate long-term because the portion of the drug that is not absorbed for skin repair remains on the skin’s surface, which can provoke continuous reactions. Along with irritation, these reactions can include redness, dryness, and exfoliation. For some patients, these continuous reactions can even break down the skin’s barrier function, creating skin sensitivity. These side effects explain why many patients abandon treatment with retinoic acid.

To avoid these problems, I now recommend that patients use retinoic acid for no longer than five months. That is sufficient time to accomplish general skin repair, without risking long-term skin reactions. After five months, I switch my patients to an agent with specific skin repair functions, such as retinol. For normal to dry skin, it improves barrier function while also stimulating and stabilizing the skin. Because retinol is converted intracellularly to retinoic acid, it leaves no free, unused retinoic acid on the skin’s surface to provoke reactions.

All the cases outlined above share key similarities. Although each patient began treatment under a doctor’s care, they later purchased medical-grade hydroquinone, and other medical-grade ingredients, through online and other unauthorized sources selling at deep discounts. The ready availability of these products, often from websites owned by physicians, pharmacies or other retailers, enabled consumers to use these products without physician oversight for more than five years continuously. Accordingly, I oppose selling medical-grade products on the Internet if they are being offered for the purpose of treating skin conditions without medical supervision. I believe the FDA should intervene to halt such practices.

Conversely, I believe that formulations combining hydroquinone with botanical anti-inflammatory agents and antioxidants that can suppress skin inflammation induced by factors such as sun exposure, hormones, and diet are very helpful in treating hyperpigmentation. Even systemic inflammatory agents such as ibuprofen can accelerate a patient’s response to hydroquinone. They do this by arresting or suppressing chronic skin inflammation.

However, in my view, adding vitamin C or glycolic acid to hydroquinone offers no scientifically documented extra benefits. In fact, vitamin C and glycolic acid can irritate the skin, which leads to inflammation and worsening of existing hyperpigmentation (rebound hyperpigmentation).

PULSED REGIMEN REDUCES RISKS
In conclusion, hydroquinone is safe and effective when used as directed by a physician for a wide variety of pigmentation problems. To increase its efficacy and avoid unwanted side effects, dermatologists should consider the following protocol:

- Prescribe hydroquinone concentrations no higher than 4%.
- Require patients using hydroquinone to use proper sun protection.
- Continue prescribing hydroquinone for no more than four to five months.
- Allow the skin to rest and restore itself for two to three months after hydroquinone therapy.
- Resume hydroquinone therapy, if needed, only after such a break.

Adopting the pulsed approach will spare our patients from the disfiguring and needless side effects of extended, self-directed use of hydroquinone.

Dr. Obagi is medical director of ZO Skin Health, Inc. He has no affiliation with Obagi Medical Products, Inc. He is a board-certified dermatologist based in Beverly Hills, California.
In this review, we examine published data reporting the efficacy of pharmaceutical agents to treat associated postinflammatory hyperpigmentation commonly seen in skin of color. Retinoids and azelaic acid have been widely used to treat acne. Now there are increasing data describing their use in skin of color for the treatment of both acne and the subsequent postinflammatory hyperpigmentation. Historically, some dermatologists have been hesitant to use retinoids in skin of color because of perceived hypersensitivity in this patient population. However, recent data support the use of retinoids and azelaic acid in skin of color as both safe and beneficial.

Azelaic acid (AzA) is a dicarboxylic acid from *Pityrosporum ovale* that inhibits tyrosinase and has cytotoxic and antiproliferative effects. A 15% gel and 20% cream are commercially available. Studies have found this agent useful in treating hyperpigmentation with acne. A 16-week, baseline-controlled study of patients with Fitzpatrick skin types IV to VI evaluated the efficacy of topical AzA gel 15% applied twice daily (n=20). Assessments at baseline and each visit included IGA of acne on a 6-point scale, total lesion count, inflammatory lesion count, noninflammatory lesion count, and IGA for PIH on a 7-point scale. At week 16, 92% of patients had a 2-point improvement in the IGA for PIH.

A multicenter, randomized, parallel-group study compared the efficacy, safety, and tolerability of AzA 20% cream to its vehicle for the treatment of facial hyperpigmentation in 52 patients with Fitzpatrick skin types IV to VI. The efficacy variables were pigmentary intensity, lesion area, and global assessment of improvement. Pigmentary intensity was measured by chromometer. Results at 24 weeks showed AzA produced significantly greater decreases in pigmentary intensity than did vehicle, as measured by both an investigator’s subjective scale (*P*=.021) and a chromometer analysis (*P*=.039). In addition, there was a significantly greater global improvement with AzA than with vehicle at week 24 (*P*=.008). The investigators concluded that AzA is an effective and well-tolerated treatment for hyperpigmentation in darker-skinned patients.

**CONCLUSIONS**
PIH is an extremely common and distressing condition in patients with skin of color. A growing body of evidence suggests that retinoids are well tolerated in skin of color. Dermatologists should consider retinoids as first-line therapies to treat acne in this patient population. In addition, AzA is another acne treatment that can offer patients improvement in both acne and hyperpigmentation. Dermatologists should consider either agent when treating acne in patients with skin of color. Some of the limitations of the studies cited include most having small sample sizes, lack of colorimetric assessments in most studies, and variable measures of efficacy used. Based on this review of literature, retinoids and AzA offer excellent treatment options for acne patients with skin of color.

DISCLOSURES
The authors have no relevant conflicts of interest to disclose.

REFERENCES


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Topical Rosacea Therapy: The Importance of Vehicles for Efficacy, Tolerability and Compliance

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ABSTRACT

Many topical medications are available for the treatment of papulopustular rosacea. While treatments contain metronidazole, azelaic acid, or sodium sulfacetamide-sulfur as the active ingredient, the composition of the vehicle formulations varies widely. These vehicles come in gels, creams, lotions and foams; some ingredients are common to many vehicles, while some vehicles contain unique ingredients designed to optimize skin penetration and delivery of the active drug to its target. Vehicles can also influence tolerability, which is always a concern in patients with heightened skin sensitivity, and compliance, which is typically lower for topical treatments than oral treatments. Ideally, the vehicle of any rosacea treatment should enhance drug delivery, be nonirritating and be easy to use. Ingredients that help repair barrier function are also desirable. This review will focus on the key components of the vehicles from the most commonly used topical therapies for papulopustular rosacea and how vehicle formulations influence the delivery of active ingredient, skin barrier repair, tolerability and compliance.


Rosacea is a common facial disorder affecting approximately 16 million people in the United States.\textsuperscript{1} The facial skin of patients with rosacea is characterized by persistent erythema, visible blood vessels and often papules and pustules.\textsuperscript{2} Rosacea sufferers frequently experience skin sensitivity characterized by physical discomfort, burning sensation, facial itching, stinging and swelling.\textsuperscript{3} The lactic acid test involving application of a solution of lactic acid to the skin and assessing the subject's reaction is a validated test for determining skin sensitivity. Approximately 75 percent of patients with rosacea have a positive reaction to this test compared with <20 percent of normal subjects,\textsuperscript{4} demonstrating the prevalence of sensitive skin among rosacea sufferers. There are four main subtypes of rosacea: erythematotelangiectatic, papulopustular, phymatous and ocular.\textsuperscript{5} Available topical treatments are indicated for the treatment of papules, pustules and erythema.\textsuperscript{6}
Topical medications comprise a major component of therapy for papulopustular rosacea. Currently, only one oral medication is approved by the Food and Drug Administration for the treatment of papulopustular rosacea, a subantimicrobial dose of doxycycline (Oracea®). In contrast, there are many topical medications to choose from that vary in active ingredient and vehicle, providing dermatologists with a wide array of treatment options. Ideally, treatment should not only deliver the active ingredient to its site of action but should not further irritate the skin, and medications that are potentially acnegenic should be avoided. Formulations that calm and soothe the skin are preferable. Emollient and barrier repair ingredients are important, as these may help repair inherent barrier dysfunction.

Other features that are important when choosing a therapy are its ease of application and its effect on the appearance of the skin when used with the patients’ regular skin care routines, particularly the application of cosmetics. The ease of application and appearance of both the medication and patients’ usual cosmetic regimens have been shown to influence patients’ ratings of their overall appearance. Ideally, topical therapies should be well tolerated on oily and/or dry skin, as many patients display findings of both. A vehicle that is tolerated on both skin types allows for more flexibility of application.

It has been suggested that the vehicle of a topical therapy may account for 50 percent to 75 percent of its efficacy. A vehicle must allow penetration of the active ingredient, without damaging the skin barrier. It must deliver the correct dose, while being easy to use and well tolerated. This review will focus on commonly used topical therapies for papulopustular rosacea and the key components of their respective vehicles that influence the delivery of the active ingredient and repair of the skin barrier, and maximize tolerability. How these formulations are accepted in clinical practice will also be discussed.

**Topical Rosacea Treatments and Their Vehicles**

Three main active ingredients are found in topical rosacea therapies: metronidazole, *azelaic acid*, or sodium sulfacetamide-

**Azelaic Acid**

Azelaic acid 15% gel is a single-phase, water-based gel that uses polyacrylic acid to form a gel matrix. This gel is approximately 70% water with a lipid concentration of approximately 3%. Having a low lipid concentration requires less emulsifier, which results in fewer irritants in the formulation. Each gram of azelaic acid 15% gel (Finacea) contains 0.15 g azelaic acid, benzoic acid (preservative), disodium-ethylenediaminetetraacetic acid (EDTA), lecithin, medium-chain triglycerides, polyacrylic acid, polysorbate 80, propylene glycol, purified water and sodium hydroxide to adjust the pH.

Azelaic acid gel formulation leaves behind minimal residue, is applied easily and creates a cooling effect on the skin. Azelaic acid is micronized to particles of 1 µm to 10 µm, which allows transfollicular permeation. TEWL and corneometry measurements showed no significant changes after two weeks of azelaic acid gel 15% application, indicating that this product does not induce barrier degradation. Subject assessments of azelaic acid 15% gel were favorable for texture and feel after two weeks of daily use.

**Niacinamide**

Niacinamide, or nicotinamide, is a physiologically active amide derivative of niacin (vitamin B3) and is an essential component of metabolic pathways involved in both cellular survival and cellular death. Niacinamide appears to have multiple anti-inflammatory mechanisms of action, including inhibition of leukocyte chemotaxis, inhibition of lysosomal enzyme release, inhibition of lymphocytic transformation and antibody production, as well as inhibition of mast cell degradation. It also increases the epidermal production of ceramides, keratin and filaggrin, which assist in the skin barrier repair function.
Oral niacinamide has been used for decades for the treatment of a variety of inflammatory skin disorders. While therapeutic use of niacinamide for inflammatory skin conditions requires oral doses ranging from 1000 to 3000 mg/d, the effective topical dose has yet to be established. Topical niacinamide 4% gel has been demonstrated to improve lesions and other symptoms in acne vulgaris and acne rosacea. Niacinamide-containing facial moisturizers have been shown to reduce erythema, dryness, scaling/peeling and inflammatory lesions in patients with rosacea.

REFERENCES


A Double-Blind, Randomized Clinical Trial of Niacinamide 4% versus Hydroquinone 4% in the Treatment of Melasma

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Abstract

Background. Multiple modalities have been used in the treatment of melasma with variable success. Niacinamide has anti-inflammatory properties and is able to decrease the transfer of melanosomes. Objective. To evaluate the therapeutic effect of topical niacinamide versus hydroquinone (HQ) in melasma patients. Patients and Methods. Twenty-seven melasma patients were randomized to receive for eight weeks 4% niacinamide cream on one side of the face, and 4% HQ cream on the other. Sunscreen was applied along the observation period. They were assessed by noninvasive techniques for the evaluation of skin color, as well as subjective scales and histological sections initially and after the treatment with niacinamide. Results. All patients showed pigment improvement with both treatments. Colorimetric measures did not show statistical differences between both sides. However, good to excellent improvement was observed with niacinamide in 44% of patients, compared to 55% with HQ. Niacinamide reduced importantly the mast cell infiltrate and showed improvement of solar elastosis in melasma skin. Side effects were present in 18% with niacinamide versus
29% with HQ. Conclusion. Niacinamide induces a decrease in pigmentation, inflammatory infiltrate, and solar elastosis. Niacinamide is a safe and effective therapeutic agent for this condition.

1. Introduction
Melasma is defined as an acquired chronic hypermelanosis on sun exposed areas being most frequently found in women with III-V phototypes of Fitzpatrick. The etiology is not completely elucidated; however, the ultraviolet sunlight exposure appears to be the most significant factor [1]. The basis of the treatment is photoprotection. Diverse modalities in drug therapy have been used such as hydroquinone (HQ), which inhibits the tyrosinase enzyme activity. In spite of its serious adverse effects and moderate results in 80% of patients, HQ is considered the gold standard treatment in melasma although usually relapses after suspension [2].

Niacinamide studies have demonstrated a suppression of melanosome transfer suggesting the reduction of cutaneous pigmentation [3], but to date there has been no clinical report of this effect in melasma. There have been several reports regarding other beneficial effects of topical niacinamide on the skin, including prevention of photoimmunosuppression and photocarcinogenesis [4], anti-inflammatory effects in acne [5], rosacea [6], and psoriasis [7]. It also increases biosynthesis of ceramides, as well as other stratum corneum lipids with enhanced epidermal permeability barrier function [8]. Moreover, its antiaging effects have been demonstrated in randomized trials [9].

The guidelines to clinical trials in melasma have suggested a correct diagnosis by using at least two subjective methods (besides an objective method), a comparison with the therapeutic gold standard and an evaluation of safety outcome [10].

The aim of this work was to assess the efficacy and safety of niacinamide 4% versus HQ 4% in the treatment of melasma through subjective and objective methods.

2. Patients and Methods
This is a double-blind, left-right randomized clinical trial. The protocol was reviewed and approved by the ethic committee in our hospital, and each subject signed a written informed consent. The sample size was determined based on favorable response: 0.8 for HQ and at least 0.4 for niacinamide, with 95% IC, two tails, $\alpha$ of 0.05 and $\beta$ of 0.8.

We included 27 women with melasma attending the outpatient clinic of Dermatology Department at the Hospital Central “Dr. Ignacio Morones Prieto”, from March 2008 to February 2009.

Our inclusion criteria were women at least 18 years old without any topical, systemic, laser, and surgical treatment on face during the previous year. The exclusion criteria were pregnant and nursing women, patients with history of hypersensitivity to some of the components of the formulas of the study, and coexistence of associate diseases and other pigmentation diseases.

A history was taken from each patient, regarding age, gender, occupation, time of onset, history of pregnancy, contraceptive pills, and sun exposure.

At baseline, we obtained two 2 mm biopsies in 27 patients, one biopsy from lesioned and another one from facial not photoexposed skin; these were stained with haematoxylin and eosin to determine the general histopathological features of the epidermis and dermis.

The inflammatory infiltrate was counted manually by two independent blinded observers, using a 0.5 × 0.5 mm ocular grid and 100× magnification. The cells were counted for the entire section, and the results expressed as the number of cells per mm². The same procedure was employed to count melanocytes (Fontana Masson) and metachromatic granules (Wright-Giemsa) in mast cells. To count the epidermal melanin, we obtained a magnification of 40× to get a scanning view of the epidermis. Images were obtained from the entire 2 mm sample with a digital camera mounted on a microscope (Olympus CX 31) which was connected to a personal computer (PC). The image signals taken by the PC were evaluated using Image-Pro Plus Version 4.5 (Media Cybernetics, Silver Spring, MA, USA). With the aim of discern possible
abnormalities of melanin in melasma patients as shown before [11], or even being induced by the intervention, we perform a qualitative analysis by Raman spectrophotometry (Horiba, Jobin-Yvon T64000, Edison, NJ, USA) before and at the conclusion of the study.

Patients were randomized in a double-blind manner to receive one treatment on the left and the other on the right side of the face. They received two containers labeled right or left with 4% niacinamide (Nicomide-T cream 4%, DUSA Pharmaceuticals Inc.) or 4% HQ (Eldoquin cream 4%, Valeant Pharmaceutical). All patients were instructed to apply the correct amount of both treatments and to use a SPF 50+ broad spectrum sunscreen every 3 hours during day time.

Concomitant use of other skin care products or systemic treatments was not allowed during the study. Treatment was administered for the period of 8 weeks, with basal evaluation and followup at 4 and 8 weeks. Assessments included a skin pigment evaluation by a chromameter (CR-300: Minolta, Osaka, Japan), melasma area and severity index (MASI), physician global assessment (PGA) by an independent observer, conventional photography, and infrared thermography (Flexcam S, Infrared solutions, USA) with photographic register which mainly was used to detect irritation. All side-effects were registered. The double-blinded study was opened at 8 weeks in order to take a 2 mm biopsy in the side treated with niacinamide.

For statistical analysis, we used the Student t-test and X2, and a P value of less than 0.05 was considered significant.

3. Results

Twenty-seven female patients with melasma were included, 12 (33%) were of skin phototype IV, and 13 (48%) of type V. The pattern of melasma was centrofacial in 13 (50%), malar in 10 (37%), and mandibular in 4 (14%).

The patients age ranged from 25 to 53 years (mean, 37 years). The duration of melasma varied from 4 to 8 years (mean, 6.5 years). Family history of melasma was found in 19 (70%) patients. The most frequent precipitating factor was the sun exposure followed by pregnancy. Eight patients (29%) have used oral contraceptives.

3.1. Clinical Results

The onset average MASI score for the HQ side was 4 (5% CI, 90.9–1.8) and 1.2 (95% IC, 0.8–1.6) after eight weeks (P < 0.001). The initial MASI score for the niacinamide side was 3.7 (95% CI, 2.9–4.4) and 1.4 (95% CI, 3.3–4.7) at the end of the study (P < 0.001). The average decrease for HQ was 70% and 62% for niacinamide. This improvement was registered using conventional photography (Figures 1 and 2) with no perceptible differences between both sides.

(Figures 1 and 2)
The PGA rated the niacinamide side improvement as excellent in three patients, good in nine, moderate in seven, and mild in eight. The HQ-treated side was rated excellent in seven, good in eight, moderate in six, and mild in six patients (Figure 3). Data showed statistical significance for both treatments, HQ ($P = 0.003$), and niacinamide ($P = 0.005$).

Physicians Global Assessment in melasma patients with niacinamide versus HQ. Colorimetric assessment was performed initially and at the end of the study; we evaluated the luminosity axis ($L^*$) as well as the erythema axis ($a^*$). The lightening effect of HQ and niacinamide was apparent at 4 weeks of treatment, whereas it was more evident at 8 weeks. Colorimetric measures showed no statistical differences between both treatments (Table 1). The erythema was more intense on the side treated with HQ than with niacinamide, but it was not statistically significant. Infrared light thermography at environmental temperature of $21^\circ C$ showed a diminished temperature of $0.8^\circ C$ in both sides after treatment. There was no statistical difference between both treatments.

Changes in MASI scores and colorimetric values for 4% HQ and 4% niacinamide-treated sides in 27 patients with melasma. Mast cell counts and melanin expression initially and after treatment with niacinamide in 11 patients.

### 3.2. Histopathology Results

The biopsy samples were stained with haematoxylin and eosin for general histology, Fontana Masson to evaluate melanin pigment, and Wright-Giemsa for metachromatic granules in mast cells. At baseline, we found a moderate to severe degree of rete ridge flattening and epidermal thinning in 23 (85%) melasma samples. Solar elastosis was present in all melasma samples. Mild to moderate perivascular lymphohistiocytic infiltrates were also present in all of them and moderate presence of mast cells near elastotic areas in 11 (40%) patients. With Fontana-Masson stained sections, the amount of melanin was increased in all epidermal layers of melasma skin; we observed pigment basal cells protruded into the dermis in 20 (74%) biopsies as informed before [12]. In the upper dermis, we found scattered melanin in 19 (70%) melasma biopsies. The features in the biopsies of nonexposed sun skin were close to normal skin.

After 8 weeks of treatment, the blind was opened in order to take a biopsy from the side treated with niacinamide. We obtained 11 posttreatment biopsies for analysis. By means of digital analysis of biopsies images, we could observe that the amount of epidermal stained melanin was diminished significantly ($P < 0.0007$). The average inflammatory infiltrate of mast cells was reduced from 22 to 16 cells/mm² ($P = 0.01$). Solar elastosis was also reduced, but no statistical differences were present (Figure 4).
Epidermal pigmentation reduction. (a) Basal melasma skin biopsy, (b) skin biopsy posttreated with niacinamide. (Fontana Masson, original magnification 40x). Below is shown the measured positive areas for melanin using a computer-assisted image analysis...3.3. Spectrophotometry

Raman spectroscopy measurements showed that the molecular structure of melanin was normal and remained unaltered after exposure to niacinamide since the measurements showed the characteristic peaks of melanin previously published [11, 12]. Patients with abnormal melanin could respond differently to treatment and explain the variable success rate to HQ [11]. We wanted to show that these patients were homogeneous in this aspect.

3.4. Side Effects

Side effects were present in the niacinamide side in 5 patients (18%), compared to 8 patients (29%) for the HQ side. The most frequent side effects were erythema, pruritus, and burning. Most of them were mild for niacinamide and moderated for HQ. On the niacinamide side, erythema, pruritus, or burning was present in 2 (7%) patients, and on the HQ side they were present in 5 (18%) patients. All these were reduced through continuous treatment in both modalities, as the a* colorimetric value did not show significant changes for both treatments at the end of the study.

4. Discussion

Melasma is a chronic and persistent hyperpigmentation, representing a therapeutic challenge because of the high rate of relapses. This work showed that niacinamide 4% is an effective agent for the treatment of melasma, as assessed by objective methods and clinical evaluation. Our results indicate that 4% niacinamide was effective in approximate 40% of patients, showing outstanding clinical results. In the posttreatment biopsies, we could observe that the amount of epidermal melanin and inflammatory infiltrate was diminished significantly, as well as solar elastosis although it was not enough to get statistical difference. This insufficient antiaging effect could be related to the short time of the study; therefore, further clinical studies using niacinamide for longer periods are warranted in this condition. We observed that the evolution time of melasma did not affect the response to treatment. On the other hand, colorimetric assessment showed no statistical difference between these two treatments ($P = 0.78$). However, the lightening effect of
HQ was evident as early as the first month of treatment, whereas with niacinamide was noted at second month. HQ had the disadvantage of moderate adverse effects in 18% of patients, compared to milder in 7% with niacinamide. Treatment with niacinamide showed no significant side effects and was well tolerated; therefore, it could be used for longer periods, as part of the initial hyperpigmentation treatment and as maintenance drug. However, further trials are required to assess the combination of this topical drug with others agents and assess its additive effects in the treatment of melasma. The mechanism of action of niacinamide in melasma could be through the reduction of melanosomes transfer [3], photoprotection actions [4], its anti-inflammatory properties [5], and a direct or related antiaging effects such as reduction of solar elastosis [9]. We previously have described prominent infiltrates of mast cells in the elastotic areas of melasma skin [1] and evidence of damage to epidermal basal membrane, which could facilitate the fall or the migration of active melanocytes and melanin into the dermis allowing the constant hyperpigmentation in melasma [13]. Due to these findings, we wanted to prove an intervention capable of inducing modifications to these atypical findings related in the pathogenesis of melasma, in addition to modify the increased pigmentation. Therefore, we propose niacinamide as an effective, integral, and safe therapeutic alternative in the melasma treatment, since it not only reduces pigmentation and inflammation, but also may reduce solar degenerative changes with minimal adverse events.

References
Comparison of topical 5% nicotinamide gel versus 2% clindamycin gel in the treatment of the mild-moderate acne vulgaris: A double-blinded randomized clinical trial

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Abstract

Background:
Acne vulgaris is considered one of the most common disorders for which patients seek dermatologic care. In the current study, we evaluated efficacy of the 5% nicotinamide gel versus 2% clindamycin gel in the treatment of the mild-moderate acne vulgaris.

Materials and Methods:
This was a randomized, controlled clinical trial that was performed in 2009-2010. Sixty female patients with mild or moderate acne vulgaris were recruited to be treated either with 5% nicotinamide or 2% clindamycin gel for 8 weeks. Acne severity index (ASI) was used to evaluate response to treatment and SPSS software was used to analyze the data.

Results:
The mean of ASI at the baseline was 16.85 ± 8.5 and 18.2 ± 12.27 in nicotinamide gel and clindamycin gel, respectively ($P > 0.05$). The mean of ASI was significantly decreased compared with baseline ASI during the time in both groups ($P < 0.0001$). However, there was not a significant difference regarding reduction of ASI between the nicotinamide and clindamycin gel ($P = 0.583$).
Conclusion:

Five percent nicotinamide gel is as effective as 2% clindamycin gel for treatment of mild to moderate acne vulgaris. No side effect was observed during the treatment.

Keywords: Acne, clindamycin, nicotinamide, treatment

INTRODUCTION

Acne vulgaris is considered one of the most common disorders for which patients seek dermatologic care. Affecting the majority of the adolescent population, acne vulgaris remains prevalent in adults, with up to 40-50% of men and women in their 20s and 10-20% in their 40s reporting acne, accounting for at least 5-6 million visits to physicians a year.[1]

Major factors contributing to the acne vulgaris include sebum secretion, abnormal desquamation of follicles, bacterial growth, and associated inflammation. New molecular and clinical studies have advanced knowledge in areas such as sebocyte biology, the role of androgens, nicotinamide, dietary factors, and the effect of cytokines, and toll-like receptors, helping identification of potential new targets for acne therapy.[1]

For a long-time, topical and systemic antibiotic along with retinoid have been the mainstays of treatment for acne vulgaris. However, overuse of oral or topical antibiotics may contribute to the development of bacterial resistance, as well as side effects such as diarrhea, yeast infections, and photosensitivity. Therefore, alternative treatments, such as nicotinamide, have been suggested for treatment of the acne vulgaris.[2]

Other medications that have been used for treatment of acne vulgaris include agents such as azelaic acid, salicylic acid, cyproterone actate, tea tree oil, and etc.[3,4,5,6]

The previous studies had used 4% nicotinamide gel for treatment of the acne vulgaris. In the current study, we evaluated efficacy of the 5% nicotinamide gel versus 2% clindamycin gel in the treatment of the mild-moderate acne vulgaris as randomized
MATERIALS AND METHODS
This was a randomized, controlled clinical trial that was performed in 2009-2010 in St-Alzahra hospital, Isfahan University of Medical Sciences, Isfahan, Iran (Registration No. = 385171).

In this study, 60 female patients with mild or moderate acne vulgaris were recruited to be treated either with 5% nicotinamide or 2% clindamycin gel. Mild acne was defined as the presence of non-inflammatory lesions (including closed or open comedones), and the number of the papules, and pustules to be <10 without any nodules or cysts.[3]

Moderate acne was defined as the presence of non-inflammatory lesions (including closed or open comedones) and the number of the papules and pustules to be <20 without any nodules or cysts.

Patients who had received any topical or oral medication for acne vulgaris in the last 1 month was excluded from the study. Patients with history of allergy to the clindamycin or nicotinamide or history of renal, hepatic or endocrine disorders were excluded from the study. Furthermore, pregnant and nursing patients or those who use oral contraceptive pill (OCP) were considered as the exclusion criteria for this study.

Informed consent was obtained from all the patients. At the baseline, demographic characteristic of the patients was obtained and recorded in especial questionnaires. For determination of acne severity, acne severity index (ASI) was calculated for each patient as following:

ASI: (2* pustules) + papules + (1/4* comedones).[3]

Reduction of ASI less than 30% was considered as weak response, 30% to 60% reduction was considered as moderate response and more than 60% reduction was considered as excellent response.
Five percent nicotinamide gel and 2% clindamycin gel were provided by Isfahan Pharmacy School in the same containers, but with different labels of A and B. Both physicians and patients were blinded to the type of treatment and the patients had been allocated randomized and instructed to apply the drug twice daily for a period of 8 weeks. Patients were visited every 2 weeks in this period of time and the ASI score of the patients along with patient satisfaction and presence of side effects were recorded. At the end of study, the codes were revealed and the collected data was analyzed using SPSS (version 18) for Windows and statistical tests including, \( t \)-test and ANOVA and Fisher exact test.

**RESULTS**

Overall, 60 patients (30 patients in the nicotinamide gel and 30 patients in the clindamycin gel) were evaluated in this study. No one was excluded from the study and all of the patients completed the study. The mean of age in nicotinamide gel and clindamycin gel were 20.83 ± 3.34 years and 21.17 ± 3.53 years, respectively, and this difference was not statistically significant \( (P > 0.05) \).

The mean of ASI at the baseline was 16.85 ± 8.5 and 18.2 ± 12.27 in nicotinamide gel and clindamycin gel, respectively, and this difference was also not statistically significant \( (P > 0.05) \).

The mean of ASI was continuously decreased during the visits in both groups and this reduction (final visit vs. baseline) was statistically significant as compared with baseline ASI in the both groups \( (P < 0.0001) \) [Table 1].

<table>
<thead>
<tr>
<th>Group</th>
<th>Baseline</th>
<th>Week 4</th>
<th>Week 6</th>
<th>Week 8</th>
<th>( P ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nicotinamide</td>
<td>16.49</td>
<td>12.77</td>
<td>9.79</td>
<td>4.39</td>
<td>(&lt;0.0001)</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>18.27</td>
<td>12.64</td>
<td>9.35</td>
<td>7.65</td>
<td>(&lt;0.0001)</td>
</tr>
</tbody>
</table>

**Table 1**

Comparison of acne severity index in the two groups during the treatment with nicotinamide and clindamycin gel.

However, Fisher exact test showed that there was no significant
difference regarding reduction of ASI between the nicotinamide and clindamycin gel \((P = 0.583)\) [Table 2].

<table>
<thead>
<tr>
<th>Group</th>
<th>Week 2</th>
<th>Week 4</th>
<th>Week 6</th>
<th>Week 8</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nicotinamide gel</td>
<td>72.31</td>
<td>70.1</td>
<td>52.5</td>
<td>87.72</td>
<td>0.583</td>
</tr>
<tr>
<td>Clindamycin gel</td>
<td>86.06</td>
<td>63.73</td>
<td>80.0</td>
<td>77.52</td>
<td></td>
</tr>
</tbody>
</table>

Table 2
Comparison of mean reduction of acne severity index by percent in the 2 groups during the treatment with nicotinamide and clindamycin gel

**DISCUSSION**

Nicotinic acid (niacin) and niacinamide (nicotinamide) are similarly effective as a vitamin because they can be converted into each other within the organism. It has been shown that topical application of niacinamide has a stabilizing effect on epidermal barrier function, seen as a reduction in transepidermal water loss and an improvement in the moisture content of the horny layer. Niacinamide can lead to increase in protein synthesis, have a stimulating effect on ceramide synthesis, speed up the differentiation of keratinocytes, and raise intracellular NADP levels. In addition, topical application of niacinamide improves the surface structure, smoothes out wrinkles and inhibits photocarcinogenesis and therefore, is effective in ageing skin. Its anti-inflammatory effects in acne, rosacea, and nitrogen mustard-induced irritation have also been suggested.[7]

The use of nicotinic acid for treatment of the acne vulgaris goes back to 1955, when it was used for its effect as counteracting iodide aggravation in acne vulgaris.[8] Treatment of acne vulgaris with nicotinic acid induced vasodilatation was described by Marchand in the same year.[9]

However, the first study that used nicotinamide gel for treatment
of acne vulgaris as a double-blind clinical trial was performed by Shalita et al. In their study, the safety and efficacy of topically applied 4% nicotinamide gel was compared against 1% clindamycin gel for the treatment of moderate inflammatory acne vulgaris. Seventy-six patients were randomly assigned to apply either 4% nicotinamide gel or 1% clindamycin gel twice daily for 8 weeks. After 8 weeks, both treatments produced comparable ($P = 0.19$) beneficial results in the Physician's Global Evaluation of Inflammatory Acne; 82% of the patients treated with nicotinamide gel and 68% treated with clindamycin gel were improved. Both treatments produced statistically similar reductions in acne lesions, and acne severity. The authors concluded that 4% nicotinamide gel is of comparable efficacy to 1% clindamycin gel in the treatment of acne vulgaris.[10]

In contrast, another research carried out by Sardesai and Kambli showed no benefit in combination of nicotinamide with clindamycin in the treatment of the acne. A total of 75 patients with inflammatory acne vulgaris were divided into three groups. Group A was treated with combination of 4% nicotinamide and 1% clindamycin combination, Group B was treated with plain 1% clindamycin and Group C, which was considered to have resistance to local antibiotics due to no response to treatment was treated with the combination. At the end of 8 weeks, it was concluded that in addition of nicotinamide was not as much value as in treating inflammatory acne and results were some as for plain clindamycin and also the combination did not offer much relief in treatment of resistant acne.[11]

The effect of nicotinamide on facial sebum was demonstrated by Draelos et al. who showed that Topical 2% niacinamide may be effective in lowering the sebum excretion rate in Japanese individuals and casual sebum levels in Caucasian individuals.[12]

It seems that nicotinamide along with the new suggested topical and systemic therapy can be effective for treatment of the acne vulgaris.[13,14,15]

In the current study, we evaluated possibly more potent 5%
nicotinamide gel instead of usual 4% concentration and in contrast to the previous studied we compared this compound with 2% clindamycin gel instead of 1% clindamycin gel. In addition, we used a blinded protocol to have a more reliable result.

Our results clearly showed that 5% nicotinamide gel is at least as effective as 2% clindamycin gel for treatment of mild to moderate acne vulgaris. Moreover, we observed no side effect during the treatment and the patients tolerated the treatment very well. Considering these results along with the anti-inflammatory effects of the nicotine amid that may help to reduce post acne erythema and its anti-pigmentary effect that may help to reduce the severity of post-inflammatory hyperpigmention after acne may suggest 5% nicotinamide gel as an appropriate treatment for acne vulgaris.

To better evaluate the efficacy of 5% nicotinamide gel in the treatment of the acne vulgaris, more randomized clinical trial (RCT) with higher number of the patients and longer follow-up is recommended.

**Footnotes**

**Source of Support:** Nil

**Conflict of Interest:** None declared.

**REFERENCES**
2. Niren NM. Pharmacologic doses of nicotinamide in the
12. Draelos ZD, Matsubara A, Smiles K. The effect of 2%

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