Azelaic Acid is an Effective and Safer Alternative to Hydroquinone in Treating Mild to Moderate Melasma in Women

Elizabeth Schmidt

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Abstract
Background: Hydroquinone has been the gold standard in treating melasma, but it does not come without possible adverse events, which include leukoderma and ochronosis, both of which may be irreversible. Furthermore, hydroquinone has been banned in Europe and Asia due to adverse events and toxicity. Azelaic acid may be an alternative to hydroquinone and boasts not only skin lightening properties but bacteriostatic, keratinolytic, and antioxidant capacities as well. Can azelaic acid be a safer option with comparable efficacy in the treatment of melasma?

Methods: An exhaustive search of available medical literature was conducted using MEDLINE- Ovid, CINAHL, Web of Science, and International Pharmaceutical Abstracts using the keywords: hydroquinone, dicarboxylic acids, azelaic acid, melanosis, melasma, melanosis drug therapy, and dermatologic agents/therapeutic use. Articles which met the clinical question and inclusion criteria of studies evaluating human participants and articles written in the English language were evaluated for quality using Grading of Recommendations, Assessment, Development and Evaluation (GRADE).

Results: Three articles met eligibility criteria. In all three articles, azelaic acid was found to be at least as effective as hydroquinone. Two studies were double-blinded and one was an open label trial where the evaluators were blinded. The two double-blinded studies had a large sample size of over 300 patients, whereas in the open label clinical trial the authors noted some limitations in that there was a small sample size of 29 patients. Overall, the quality of the studies was moderate to low due to limitations.

Conclusion: The studies suggest that azelaic acid applied twice daily along with a broad spectrum sunscreen is as effective with less chance of adverse side effects than hydroquinone therapy for the treatment of melasma.

Keywords: Hydroquinone, dicarboxylic acids, azelaic acid, melanosis, melasma, melanosis drug therapy, and dermatologic agents/therapeutic use.

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Biography

Elizabeth Schmidt is originally from South Florida and received her Bachelor of Science degree from Florida Atlantic University (FAU), in 2010, with a major in Biology. Her clinical background is working in chiropractic medicine as a medical assistant. She is interested in pursuing a career in dermatology.
Abstract

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List of Abbreviations

AZA………………………………………………………………Azelaic Acid
HQ............................................................................................... Hydroquinone
MASI……………………………………………………………Melasma Area Severity Index
Azelaic Acid is an Effective and Safer Alternative to Hydroquinone in Treating Mild to Moderate Melasma in Women

BACKGROUND

Even toned skin color is considered a universal sign of youth and beauty.¹ When skin pigmentation disorders occur, they can be associated with psychological impacts.² Melasma is an acquired light to dark brown hyperpigmentation that most often occurs in sun exposed areas of the skin, most commonly on the face. Melasma can be associated with pregnancy, oral contraceptive use, phototoxic drugs, and antiseizure medications. Although, sun and UV radiation are the most common etiologic factors.³ Of the patients that suffer from melasma, 90% are women. It is also much more common in women during their reproductive years.² The melasma lesions are usually symmetric with irregular borders. The most common locations are the cheeks, upper lips, chin, and forehead. Melasma may affect any race, but it is more prevalent in darker skin types, which include Fitzpatrick types IV-VI. Notably, melasma is the most common pigmentary skin disorder among South East Asians. It is also common among Hispanics and Asians who live in areas of intense solar UV radiation.²

The pathophysiology of melasma remains uncertain, but several factors have been implicated. Increased estrogen has been suggested because of the increased frequency of melasma during pregnancy, in patients using oral contraceptives, and patients using estrogen replacement therapy. Melasma may be induced by estrogen due to the presence of estrogen receptors on melanocytes. This may stimulate the melanocytes to produce more melanin.²

The most commonly prescribed pigment-lightening agent is currently hydroquinone (HQ). Although it has proved effective in treating melasma, there is some controversy regarding
this compound. HQ is considered the gold standard for hyperpigmentation treatment in the United States. However, since its inception predated that of the Food and Drug Administration, many formulations have not been studied for efficacy and safety. A ban is being considered in the United States as well. HQ can be found in 2% concentration in over-the-counter preparations and 4% concentration available as a prescription.¹

HQ is a phenolic compound that functions by inhibiting the enzymatic oxidation of tyrosine.¹ Issues with the topical toxicity of HQ are related to the fact that it is a strong oxidant that is rapidly converted into melanocyte toxic products. These byproducts may cause depigmentation.¹ Adverse reactions of HQ are associated with the dose and the length of treatment. Irritation is the most common adverse reaction. Other adverse reactions include erythema, stinging, colloid milium, irritant and allergic contact dermatitis, nail discoloration, transient hypochromia, and paradoxical post-inflammatory hypermelanosis. The so-called ‘confetti-like’ depigmentation or guttate hypomelanosis is characterized by mottles depigmented spots that develop on the macules of melasma and is seen in patients using HQ at concentrations higher than 2%.² It has long been known that HQ can cause ochronosis.¹ Furthermore, HQ is non-specific for just the hyper-pigmented skin. It can also lighten normally pigmented skin. Repeated application can cause leukoderma or vitiligo-like hypochromia.⁴

The adverse reactions associated with HQ have raised questions of safety and HQ has since been banned in Europe and Asia. Alternative topical agents for melasma need to be considered. Azelaic acid (AZA) is a topical prescription medication that was first developed to treat acne because it boasts keratinolytic and bacteriostatic properties.² It is also approved for treatment of acne rosacea.¹ AZA is a naturally occurring, nonphenolic, saturated, nine-carbon
dicarboxylic acid that competitively inhibits tyrosinase.\textsuperscript{2} It may also interfere with DNA synthesis. Unlike HQ, topical AZA has no depigmentation effect on normally pigmented skin \textsuperscript{2} and it specifically targets abnormal melanocytes.\textsuperscript{1} Free radicals in the skin are said to contribute to hyperpigmentation; AZA helps reduce free radical formation.\textsuperscript{2} AZA does not cause systemic toxicity, allergic sensitization, or photosensitization.\textsuperscript{3} AZA may cause short-lived stinging when applied in some individuals,\textsuperscript{1} but there are no noteworthy adverse side effects apart from an initial and transient irritation\textsuperscript{3} and pruritus, mild erythema, and burning.\textsuperscript{2} Because AZA does not affect normal melanocytes and fibroblasts, leukoderma or exogenous ochronosis are not connected to its use. AZA is currently available as a 15\% cream/gel and a 20\% concentration. The nontoxic properties of AZA pose an advantage in the long, frequently repeated treatment of melasma.\textsuperscript{5}

Given the concerns regarding HQ along with the side effects, AZA, which boasts little to no side effects with good hyperpigmentation lightening activity, may be a preferable therapy to hydroquinone in the treatment of mild to moderate melasma in women.

**METHODS**

An exhaustive search of available medical literature was conducted using MEDLINE-Ovid, CINAHL, Web of Science, and International Pharmaceutical Abstracts using the keywords: hydroquinone, dicarboxylic acids, azelaic acid, melanosis, melasma, melanosis drug therapy, and dermatologic agents/therapeutic use. Articles which met the clinical question and inclusion criteria of studies evaluating human participants and articles written in the English
language were evaluated for quality using Grading of Recommendations, Assessment, Development and Evaluation (GRADE).  

RESULTS
The initial search yielded 34 articles for review. After eliminating duplicates and screening these results for relevant articles using eligibility criteria, there were a total of 3 articles, which were all randomized controlled clinical trials. Two of the articles were double-blinded, and one was an open label clinical trial. See Table I.

Farshi et al
This study was an open label clinical trial that took place over a period of 2 months. The study protocol conformed to the guidelines of the 1975 Declaration of Helsinki and was approved by the Medical Ethics Committee of Iran University of Medical Sciences. All patients gave informed consent before being recruited for the study. Women with melasma were chosen from the dermatology clinic of Hazrat Rasoul Hospital, Iran University of Medical Sciences.

The study inclusion criteria required a 6 months or longer diagnosis of epidermal melasma via Wood’s lamp examination. All patients included in the study were without treatment of their melasma for at least 2 months before the start of the study. Exclusion criteria included patients taking oral contraceptives or corticosteroid therapy, those patients with a history of endocrine disorders, and pregnant and lactating women. At the initial visit, all the participants’ underwent an extensive medical history which gathered information regarding the time of onset, history of pregnancy, oral contraceptive use, sun exposure, drug history, and other factors associated with melasma. In addition, the type of melasma was assessed by a Wood’s lamp
examination. Each patients’ melasma was assigned a clinical pattern of centrofacial, malar, or mandibular, and Wood’s lamp was used to assess if the melasma was epidermal, dermal, or mixed. Only the epidermal melasma patients were included in the study.⁴

Patients were randomized to receive either 20% azelaic acid (AZA) or 4% hydroquinone (HQ) cream. Patients were instructed to apply the topical medication twice daily for 8 weeks. All patients were required to apply a broad spectrum standardized sunscreen to their entire face, and they were instructed to reapply every 3 hours. The evaluators clinically evaluated the patients at 1 month and again at the 2 month mark. The evaluators were blinded to the study medication. Color photos were taken at baseline, at 1 month, and at the 2 month mark, which represented the end of the study period. Response to treatment was evaluated using the Melasma Area Severity Index (MASI) score. The clinical evaluation was assembled into 4 categories: no effect (no visible changes in pigmentation), mild (decrease of visible pigmentation, but there is still some visible border), moderate (marked decreased of visible pigmentation, but there is still some visible border), or excellent (a complete loss of visible abnormal pigmentation). Patients rated the severity of skin erythema, dryness, itching, burning, irritation, and hyperpigmentation on a scale from 0 (none) to 4 (severe). These same side effects were also evaluated by the evaluators.⁴

Overall, 40 patients with melasma were evaluated for inclusion in the study, all of which were women. Of the 40, 30 met the inclusion criteria and, in turn, were enrolled. One patient from the AZA group dropped out at 2 weeks. Therefore, the results are based off of 29 patients who completed the study. Fifteen patients were treated with HQ (51.7%) and 14 patients were treated with AZA (47.3%). All the women had epidermal melasma that was distributed in the following clinical patterns: centrofacial n=21 (72.4%), malar n=7 (24.1%), mandibular n=1
(3.4%). The mean age of the studied patients was 34.6 years (34.6 +/- 6.6) (mean +/- SD). The mean duration of the disease was 4.1 years (4.1 +/- 2.9). 20 (69%) patients had a history of oral contraceptive use.\textsuperscript{4}

The mean MASI score before therapy was 7.4 (7.4 +/- 3.3). The mean MASI score after 1 month of treatment was 6.5 (6.5 +/-3.3) and after 2 months it was 5.04 (5.04 +/- 3.4). The decrease in the MASI scores after 1 and 2 months’ treatment was statistically significant (paired t-test, P < 0.001 where P of 0.05 or less was considered significant). At baseline in the HQ group, the mean MASI score was 7.2 +/- 3.2 and 7.6 +/- 3.5 in the AZA group. There was no statistical difference found between them (t-test, CI 95% = -2.9 to 2.2). At the 1 month mark, the mean MASI score for the HQ group was 6.7 +/- 3.4 and 6.3 +/- 3.4 in the AZA group. There was no significant difference noted between them (t-test, CI 95% = -2.2 to 3). After 2 months of treatment, the HQ groups’ MASI score was 6.2 +/- 3.6 and the AZA groups’ was 3.8 +/- 2.8. This showed a significant statistical difference (t-test, CI 95% = 0.03 to 4.9). The overall adverse effects of the topical medications in this study were mild and transient, but the side effects of HQ proved to be more severe than those of AZA.\textsuperscript{4}

Table II depicts the objective assessment of pigmentary responses in both the HQ and AZA groups. Comparison of the pigmentary response in the 2 groups showed a significant difference only at the 2 month mark. Adverse reactions can be compared in Table III.

\textbf{Balina et al}

This study\textsuperscript{5} enrolled 329 non-pregnant, non-nursing women with an epidermal or mixed epidermo-dermal type of melasma. There were 70% of the patients who ceased oral contraceptive use before treatment, and 30% of the patients who remained on oral contraceptives
during treatment. Patients were randomly assigned to treatment with either AZA 20% cream (n=164) or with HQ 4% (n=165). Patients were instructed to apply topical treatment twice a day for 24 weeks. The use of a sunscreen was mandatory.  

Patients were examined at baseline and at 4, 9, 14, 19, and 24 weeks of treatment. At each follow-up, the lesion size was determined planimetrically, and the pigmentary intensity, as compared to the nonaffected skin, was rated on a 5 point scale (1= no difference, 5=intensely more pigmented). At the final visit, the overall response to treatment was rated as excellent, good, fair, or poor.  

The patients in each study group were well matched with regard to age, race, type, and duration of melasma. The median age in the AZA group was 35 years old and 34 years old in the HQ group. The median previous duration of melasma in both groups was 4 years. The number of patients previously treated in the AZA group was 71 and 78 in the HQ group. There were 74.7% of patients with melasma in the AZA group and 71.2% in the HQ group. The AZA group had 25.3% of the patients with mixed type of melasma and 28.2% in the HQ group.  

One hundred and twenty two female patients (74.4%) of the AZA group and 121 females (73.3%) of the HQ group completed the full 24 weeks of treatment. Six patients in each treatment group discontinued therapy because of local side effects, which including burning, itching, and erythema. The remainder of those that did not complete the study were lost to follow-up due to reasons not related to therapy or because of poor compliance (mainly between weeks 4 and 9 of treatment). A reasonable overall rating was not possible in those cases.  

At the study’s conclusion at 24 weeks, 79 patients (64.8%) of the AZA group and 87 patients (72.5%) of the HQ group had achieved good or excellent overall result, whereas 9
patients (7.4%) in the AZA and 10 patients (8.3%) in the HQ group achieved poor results (Figure I). Local adverse events mostly remained mild and transient. Itching proved to be the most prominent symptom (AZA=12/HQ=18), followed by burning (AZA=10, HQ=18).\textsuperscript{5}

The time course and magnitude of median lesion size reduction was similar in both groups: 71% for AZA group and 78% for HQ group. 72 AZA patients (60%) and 80 HQ patients (66%) achieved a reduction in initial lesion size by greater than 50%. With respect to the pigmentary intensity, a reduction by 1 to 3 levels was noted in 84.2\% of the patients in the AZA group and 89.2\% of the patients in the HQ group (Table IV). Additionally noted in Table IV, there was a noticeable lightening effect in the drop-out patients as well. It is also important to point out that there was no discernable difference in treatment effect in those patients who remained on oral contraceptives as opposed to those who stopped oral contraceptive therapy before the study. For example, 73\% of the oral contraceptive users in the AZA group and 75\% of those in the HQ group achieved a good or excellent result. Moreover, there was no observable correlation between skin type, race, and response to treatment.\textsuperscript{5}

\textbf{Sivayathorn et al}

This study\textsuperscript{7} included 340 patients with epidermal or a mixed epidermal-dermal type of melasma plus 4 additional cases of uncertain diagnosis in a 24 week double-blind study. The melasma type was determined via Wood’s lamp examination. The breakdown of patients in each group was as follows: epidermal, AZA=109, HQ=116; epidermo-dermal, AZA=56. HQ=55. Patients with dermal type melasma were not included in the study because no treatment effect was expected once the pigment had dropped into the dermis. Pregnant or nursing patients were
excluded. Only patients who had no prior history of oral contraceptive use or who had not been using oral contraceptives for at least 6 weeks prior starting treatments were eligible.7

The patients were randomly placed into groups receiving a twice daily treatment with either AZA 20% (n=167) or HQ 2% cream (n=173). Patients were required to wear a broad spectrum sunscreen over the entire study period. No other treatments for melasma were allowed. If patients were using other treatments for their melasma, a 2-week wash out period was established before the study medication was given. Both of the treatment groups were matched well with regard to skin type, age, type and duration of melasma.7

Patients were examined at baseline and after 4, 9, 14, 19, and 24 weeks of treatment. The main criteria for the effectiveness of treatment was the physician’s overall rating of the therapeutic results at the end of treatment, which includes the patient’s last follow-up regardless of the actual duration of therapy. The physician’s overall rating included “excellent,” “good,” “moderate,” or “poor.” The secondary criteria for effectiveness of treatment included the classified percentage improvement, which was as follows: <25%, 25-50%, 50-75%, and > 75%, the size of the macules, and the rating of pigmentary intensity. The size of the melasma lesion(s) was measured by tracing the outline onto a plastic sheet followed by planimetrical evaluation. The pigmentation intensity was evaluated in relation to the unaffected facial skin. This assessment was made through visual inspection and rated on a 5-point scale. The 5-point scale is as follows: 1= no difference, 2= slightly darker, 3= moderately darker, 4= markedly darker, 5= very markedly darker. The level or reduction in the pigmentary intensity was calculated by comparison with the baseline rating.7
Of the patients who met the inclusion criteria and who were admitted into the study, 7147 (88%) in the AZA group and 153 (88.4%) in the HQ group completed the full 24 weeks course of therapy. In the majority of the 40 drop outs, discontinuation was not related to the study medication (AZA: 11/20, HQ: 14/20). In the AZA group, 5 patients dropped out due to local side effects. In the HQ group, 2 patients dropped out because of local side effects. Four patients of each group dropped out because of poor efficacy or lack of compliance. In the investigator’s overall assessment at the end of treatment (including the drop outs) the effectiveness was rated as excellent or good in 111 AZA patients (68.9%) and 73 HQ patients (43.7%). Moderate improvement was achieved in 33 (20.5%) and 58 (34.7%) of the AZA and HQ groups (Figure II). For those patients who completed the 24 weeks of treatment, excellent or good results were obtained in 75.5% of the AZA patients and 47.1 of the HQ patients. A moderate response was noted in 31 AZA patients (21.1%) and in 57 HQ patients (37.3%).

A high improvement rate was found more frequently in the AZA group as opposed to the HQ group. For example, 68.8% of the AZA patients compared with 54.7% of the HQ patients improved by more than 50% (Table V). Over the treatment period, the median lesion size decreased from 62cm^2 to 41cm^2 in the AZA group and from 61cm^2 to 34cm^2 in the HQ group (Table V). In the majority of the patients, the melasma at baseline was rated markedly to markedly more pigmented than the unaffected skin. At the end of treatment (including the drop outs), the distribution of AZA patients with a “lightening” (86.3%) and “no lightening” (13.7%) of the melasma trumped that of the HQ patients with a “lightening” (78%) and “no lightening” (22%). It is also important to note that similar rates of overall excellent and good results were obtained with AZA cream in both epidermal and mixed epidermo-dermal melasma
patients at 67.3% and 71.2% (Table VI). In the HQ group, the epidermal melasma responded better at 50%, whereas the mixed type achieved a 30.2% improvement. The rate of excellent and good results showed that long standing lesions responses better the AZA (0-2 years: 58.1%; > 6 years: 73.3%) than to HQ (0-2 years: 62.5%; > 6 years 34%).

Itching was the most commonly noticed symptom followed by stinging and burning sensations (27 of 61 AZA patients (44%) and 10 of 22 HQ patients (45%). The more objectively measured symptoms such as scaling (AZA 1.8% and HQ 1.7%), erythema (AZA 6.6% and HQ 5.8%) were observed at low incidence rates. Itching was the most prominent subjective symptom in the AZA group (11/15 patients).

DISCUSSION
In synthesizing the results from the three studies, the consensus was that azelaic acid (AZA) when used in conjunction with a broad spectrum sunscreen was as at least as effective as hydroquinone (HQ) cream in treating melasma. Two of the studies used a physician’s rating system as a primary endpoint of overall response to treatment and both found that AZA was as effective as HQ by achieving a good or excellent overall result. One of the studies actually found that for those who completed the full 24 weeks of therapy, AZA was superior to HQ in treating melasma through good or excellent results. The same studies referenced above used lesion size reduction as a measure of therapeutic effect of therapy. Across both study groups, similar percentages of patients in the AZA and HQ groups achieved a similar and appreciable reduction in lesion size. The same two studies used pigmentary intensity/lightening effect as a measure of effectiveness, and again, across both groups the results were very close in size. The lightening effect of AZA beat out HQ in one of the studies. The two studied being referenced
also included a well matched proportion of epidermal melasma and mixed epidermo-dermal melasma patients.\textsuperscript{5,7} One study\textsuperscript{7} found that with AZA the overall effects in both epidermal and mixed epidermo-dermal had similar overall rates of good and excellent results, whereas in the HQ group, the epidermal melasma responded better than the mixed epidermo-dermal type. The same study also found that AZA was more effective than HQ for long standing lesions (> 6 years duration). In the shorter study,\textsuperscript{4} which lasted 2 months, a significant difference was found in favor of the AZA group with respect to MASI scores. This study only included the epidermal type.

All three studies\textsuperscript{4,5,7} found that the overall adverse effects of the study medications were mild and transient. In Balina et al\textsuperscript{5} local irritation was reported more frequently in the AZA group, but allergic sensitization was only observed with HQ. Farshi et al\textsuperscript{4} showed that the adverse effect of HQ were more severe than those of AZA. None of the patients in any of the studies suffered from leukoderma or exogenous ochronosis. Exogenous ochronosis is related to HQ by way of its phenolic properties and/or to the radical degradation products of the chemical compound.\textsuperscript{7} Because AZA does not affect normal melanocytes, neither of the two adverse effects noted above are associated with its use.\textsuperscript{5} Moreover, because azelaic acid does not affect normal melanocytes, has bacteriostatic, keratinolytic, and antioxidant properties, it is also approved to treat rosacea and acne. Many women suffer from multiple skin conditions and may have melasma with adult acne and/or rosacea. AZA makes a good choice for the long-term treatment of these patients.

Across all three studies,\textsuperscript{4,5,7} each patient was required to use a broad spectrum sunscreen. Sun exposure is a trigger for melasma and for exacerbation of a pre-existing melasma condition.
Therefore, these results take into account that patients were sun protected, and physicians should make it clear that patients undergoing topical treatment for melasma need to be vigilant about sun protection during daylight hours.

In appraising the evidence in the three study articles, the limitations of the Farshi et al\(^4\) included the following: the colorimeter was not used in this study, which represents the most significant limitation of the study, only epidermal melasma types were included, and the study group was only 29 patients. Additionally, Farshi et al\(^4\) was an open label clinical trial, meaning that they did not attempt to disguise the treatment. This leans towards bias, as both the patient and the physician are aware of which groups are receiving what type of treatment, although, the evaluators were blinded to the study medication.\(^4\) This was enough to downgrade the study as noted in Table I. Only Farshi et al\(^4\) used the MASI score as an index to quantify the severity of melasma changes during therapy. The lack of use of a validated scale for assessing melasma severity/improvement was a downgrade in the other two studies (Table I).\(^5,7\) With respect to Sivayathorn et al,\(^7\) the HQ was 2% concentration as opposed to the other two studies which used 4% prescription strength HQ. A clear superiority of AZA over HQ 2% must be considered as HQ 2% preparations considered only weakly to moderately effective\(^7\) and AZA 20% is prescription strength. Only one study\(^5\) included some patients who were currently on oral contraceptives. This may represent a limitation since melasma may be induced by estrogen.\(^2\) Although, Balina et al\(^5\) did not point to relevant differences in the response of the oral contraceptive user versus non-users.

**CONCLUSION**
As HQ has been banned in Europe and Asia, alternative topical agents for melasma need to be considered. Overall, the three studies showed that AZA is at least as effective as HQ in treating melasma in women. Although, in the U.S. HQ is considered the current gold standard in melasma treatment, clinicians should consider the toxic effects associated with HQ and transition towards AZA. As noted previously, AZA does more than just reduce abnormal pigmentation in the skin. It treats acne and rosacea as well, two other common skin disorders in women. Moreover, it does not produce phototoxicity and it selective to abnormal melanocytes so the risk of leukoderma does not exist, as in HQ. The fact that HQ 2% can be purchased over the counter and AZA 20% needs to be prescribed by a clinician may pose a limitation for patients who do not have access to clinical care, yet suffer from melasma. That being said, HQ 2% does not come without the risk of adverse effects. In fact, persistent skin deformity due to exogenous ochronosis may be brought about even with HQ 2% preparations during long term use.⁵
References


### Table I: Quality Assessment of Reviewed Articles

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Downgrade Criteria</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Farshi et al</td>
<td>RCT</td>
<td>Not serious</td>
<td>Serious</td>
</tr>
<tr>
<td>Balina et al</td>
<td>RCT</td>
<td>Serious(^b)</td>
<td>Not Serious</td>
</tr>
<tr>
<td>Sivayathorn et al</td>
<td>RCT</td>
<td>Very serious(^b,c)</td>
<td>Not Serious</td>
</tr>
</tbody>
</table>

\(^a\) Small sample size  
\(^b\) Didn’t use a validated scale for assessing melasma severity  
\(^c\) Used HQ 2\% instead of HQ 4\%

### Table II. Hypopigmentation Grading in HQ and AZA groups at First and Second Follow-Up Period from Farshi et al study

<table>
<thead>
<tr>
<th>HYPOPIGMENTATION GRADING</th>
<th>FIRST FOLLOW UP</th>
<th>SECOND FOLLOW UP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HQ</td>
<td>AZA</td>
</tr>
<tr>
<td>1</td>
<td>4</td>
<td>26.7</td>
</tr>
<tr>
<td>2</td>
<td>8</td>
<td>53.3</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td>20</td>
</tr>
<tr>
<td>4</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
(1) No effect (no visible changes of pigmentation); (2) mild (decrease of visible pigmentation, but there is still some visible border); (3) moderate (marked decrease of visible pigmentation, but there is till some visible border); and (4) excellent (a complete loss of visible abnormal pigmentation)

### Table III. Adverse Events of AZA and HQ at First and Second Follow-Up Period from Farshi et al study

<table>
<thead>
<tr>
<th></th>
<th>FIRST MONTH</th>
<th></th>
<th></th>
<th></th>
<th>SECOND MONTH</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AZA</td>
<td>HQ</td>
<td></td>
<td></td>
<td>AZA</td>
<td>HQ</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>%</td>
<td>No</td>
<td>%</td>
<td>No</td>
<td>%</td>
<td>No</td>
</tr>
<tr>
<td>ERYTHEMA</td>
<td>1*</td>
<td>7.3</td>
<td>7*</td>
<td>46.6</td>
<td>0</td>
<td>0</td>
<td>2*</td>
</tr>
<tr>
<td>IRRITATION</td>
<td>5*</td>
<td>35.5</td>
<td>9*</td>
<td>59.9</td>
<td>2*</td>
<td>14.3</td>
<td>7*</td>
</tr>
<tr>
<td>PRURITUS</td>
<td>1*</td>
<td>7.3</td>
<td>3*</td>
<td>20</td>
<td>0</td>
<td>0</td>
<td>1*</td>
</tr>
</tbody>
</table>

*Grade 1; ^Represents one patient grade 2 and 8 of them grade 1

### Table IV. Reduction in pigmentary intensity from Balina et al study

<table>
<thead>
<tr>
<th>TREATMENT</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>REDUCTION*</td>
<td>AZA</td>
</tr>
<tr>
<td></td>
<td>HQ</td>
</tr>
</tbody>
</table>


Reduction levels were determined from the difference in rating of pigmentary intensity (5-point scale) before and at the end of treatment; ^ numbers in brackets refer to patients who dropped out because the result was achieved at the last follow-up visit

<table>
<thead>
<tr>
<th>Reduction Levels</th>
<th>Count</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>BY 3 LEVELS</td>
<td>6</td>
<td>10 [2]</td>
</tr>
<tr>
<td>BY 1 LEVEL</td>
<td>57 [22]</td>
<td>49 [17]</td>
</tr>
</tbody>
</table>

*Reduction levels were determined from the difference in rating of pigmentary intensity (5-point scale) before and at the end of treatment; ^ numbers in brackets refer to patients who dropped out because the result was achieved at the last follow-up visit*
Table V. Percentage improvement, reduction in pigmentation intensity and lesion size at the end of therapy from Sivayathorn et al study

<table>
<thead>
<tr>
<th>% improvement</th>
<th>AZA</th>
<th>HQ</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;= 25%</td>
<td>17 (11.0)</td>
<td>42 (26.1)</td>
</tr>
<tr>
<td>25-50%</td>
<td>31 (20.1)</td>
<td>31 (19.2)</td>
</tr>
<tr>
<td>50-75%</td>
<td>44 (28.6)</td>
<td>37 (23.0)</td>
</tr>
<tr>
<td>&gt;75%</td>
<td>62 (40.3)</td>
<td>51 (31.7)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Reduction in pigmentation intensity by:</th>
<th>N (%)</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 levels</td>
<td>11 (6.6)</td>
<td>10 (5.8)</td>
</tr>
<tr>
<td>2 levels</td>
<td>62 (37.1)</td>
<td>53 (30.6)</td>
</tr>
<tr>
<td>1 level</td>
<td>72 (43.1)</td>
<td>72 (41.6)</td>
</tr>
<tr>
<td>&lt; 1 level</td>
<td>22 (13.2)</td>
<td>38 (22)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Median lesion size (range)</th>
<th>Initial</th>
<th>Last examination</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>62cm² (2-221)</td>
<td>61cm² (0-165)</td>
</tr>
<tr>
<td></td>
<td>41cm² (3-247)</td>
<td>34.5cm² (0-247)</td>
</tr>
</tbody>
</table>

Table VI. Overall improvement rating in cases of epidermal or mixed epidermo-dermal melasma from Sivayathorn et al study

<table>
<thead>
<tr>
<th></th>
<th>EXCELLENT</th>
<th>GOOD</th>
<th>MODERATE</th>
<th>POOR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N (%)</td>
<td>N (%)</td>
<td>N (%)</td>
<td>N (%)</td>
</tr>
<tr>
<td>---------------</td>
<td>-------</td>
<td>-------</td>
<td>-------</td>
<td>-------</td>
</tr>
<tr>
<td><strong>AZA</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EPIDERMAL</td>
<td>19 (17.8)</td>
<td>53 (49.5)</td>
<td>23 (21.5)</td>
<td>12 (11.2)</td>
</tr>
<tr>
<td>MELASMA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EPIDERMODERMAL</td>
<td>7 (13.5)</td>
<td>30 (57.7)</td>
<td>3 (19.2)</td>
<td>2 (8.6)</td>
</tr>
<tr>
<td>MELASMA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>HQ</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EPIDERMAL</td>
<td>17 (15.2)</td>
<td>39 (34.8)</td>
<td>36 (32.1)</td>
<td>20 (17.9)</td>
</tr>
<tr>
<td>MELASMA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EPIDERMODERMAL</td>
<td>3 (5.7)</td>
<td>13 (24.5)</td>
<td>21 (39.6)</td>
<td>16 (27.2)</td>
</tr>
</tbody>
</table>

**Figure I:** Overall rating of the therapeutic results achieved during a 24-week treatment period from Balina et al study
(AZA 122 patients; HQ 119 patients)
Figure II. Overall rating of improvement at the end of therapy from Sivayathorn et al study

Figure III. Classified percentage improvement at the end of therapy from Sivayathorn et al study