

## Original article

**Melasma: a comparative trial of azelaic acid (20%) cream alone and in combination with tretinoin (0.1%) cream**

Ijaz Ahmad, Zarnaz Wahid,\* Mujeeb Ansari

Department of Dermatology, Ziauddin Medical University, Karachi.

\* Department of Dermatology, Dow Medical College and Civil Hospital, Karachi.

**Abstract** *Background* Melasma is a common acquired disorder of symmetrical hypermelanosis characterized by irregular, light to gray brown macules involving exposed areas of skin. Therapy for melasma is generally difficult especially in dark skin. The open comparative trial was carried out in the outpatient department of 'BISD' to compare the effect of azelaic acid (20%) cream alone and in combination with tretinoin (0.1%) cream in the management of melasma.

*Materials and methods* The study was carried out in the outpatient department of 'BISD', from 1<sup>st</sup> May 2002, till 30<sup>th</sup> April 2003, over a period of 1 year. A total of 48 patients were included in the study. The patients were studied in two groups of 24 each. The group 'A' applied azelaic acid cream (20%) twice daily i.e. in the morning and evening. The other group labelled group 'B' applied azelaic acid cream (20%) twice-daily plus tretinoin cream (0.1%) in the nighttime. The treatment was advised for a period of 6 months. For the initial 3 months, the treatment was given daily but in the remaining 3 months every alternate day. All the patients were also advised a broad-spectrum sunscreen.

*Results* Forty eight patients belonging to both sexes were included in the study, the age range being 18-40 years. There were 12 males and 36 females. In group "A", there were 5 males and 19 females, while group "B" comprised 7 males and 17 females. Significant clinical improvement i.e. excellent and good response, was observed in both the groups by the end of 6 months therapy i.e. group 'A' 17 patients (71%,  $p < 0.05$ ) and group 'B' 19 patients (79%,  $p < 0.05$ ). In group 'A', 7 patients (29%) had moderate or no response while only 5 patients (21%) in group 'B' showed mild to moderate response.

*Conclusion* Azelaic acid when used in combination with tretinoin is more effective than azelaic acid monotherapy.

**Key words**

Melasma, azelaic acid, tretinoin

**Introduction**

The color of skin is influenced by a number of factors including various pigments, blood flow and the optical properties of skin. Melanin is the major pigment responsible for imparting skin its

normal color. Melanin pigmentation of the skin is a genetically determined multistage process accounting for intrinsic racial and individual differences in skin color. Skin pigmentation is subject to a wide variety of pathological disturbances giving rise to a reduced or enhanced melanocytic activity and proliferation resulting in cutaneous hypo- or hyperpigmentation.

Melasma is a common acquired disorder of symmetrical hypermelanosis

**Address for Correspondence**

Dr. Ijaz Ahmad,  
H. No. 36/2 Khayaban E Shujaat D-H-A,  
Phase 5, Karachi.  
Ph # 021 7528910, 021 7541152

characterized by irregular, light to grey brown macules involving exposed areas of skin. It affects all the races and is predominantly a disease of women,<sup>1,2</sup> although it can occur in men, as well.<sup>3</sup> Clinicohistological features are the same in both sexes. Multiple factors are implicated in the etiology and pathogenesis of melasma.<sup>4</sup> Important etiological factors include endocrinal factors, oral contraceptives,<sup>5</sup> estrogen-progesterone therapy,<sup>6</sup> pregnancy, UV radiations,<sup>4,7</sup> genetic factors, thyroid dysfunction,<sup>8</sup> cosmetics and drugs.<sup>1</sup>

Melasma can be divided into 3 types based on Wood's light examination i.e. epidermal, dermoepidermal and dermal<sup>9,10</sup> On Wood's light examination, epidermal and dermoepidermal types show accentuation, while there is no change in the dermal type. Therapy for melasma is generally difficult especially in dark skin.<sup>11</sup> Conventional therapy for melasma consists of hydroquinone, retinoic acid, azelaic acid and topical steroids used alone or in various combinations. Recent advances include chemical peeling with various agents like trichloroacetic acid, alpha hydroxy acids, salicylic acids, alpha ketoacids, Jessner's solution, phenol, resorcinol and Baker's solution.<sup>12</sup> These may be used alone or in various combinations with variable results. Azelaic acid<sup>15</sup> as well as tretinoin<sup>2,11</sup> are used in melasma as monotherapy and in combination with other therapeutic agents.

The comparative open trial was carried out to compare the effect of azelaic acid (20%) cream alone and in combination with tretinoin (0.1%) cream in the management of melasma.

### **Materials and methods**

The study was carried out in the outpatient department of 'BISD', from 1<sup>st</sup> May 2002, till 30<sup>th</sup> April 2003, over a period of 1 year. Forty eight patients were included in the study. There were 12 males and 36 females. The age range was 18-40 years. Patients with epidermal or dermoepidermal pigmentation as determined by Wood's light examination were included in the study. Lactating and pregnant women were excluded. Only those patients were included who had not been taking any treatment for the past two months. Patients on oral contraceptive therapy or any antiepileptic drugs were also excluded. Patients with some intrinsic disease like ovarian tumors were excluded as well. The patients were divided in two groups of 24 each. Group 'A' applied azelaic acid cream (20%) twice daily i.e. in the morning and evening. Group 'B' applied azelaic acid cream (20%) twice-daily plus tretinoin cream (0.1%) at night. The treatment was advised for a period of 6 months. For the initial 3 months, the treatment was given daily but for the following 3 months on every alternate day. A broad-spectrum sunscreen was also advised to all the patients. The sunscreen was advised after the daytime application of azelaic acid cream as well as 30 minutes before going into sunlight. All the patients were followed up monthly to look for any clinical improvement and side effects. The clinical assessment was made by a decrease in the intensity of pigmentation and the size of lesions. Decrease in intensity was assessed by comparison with the surrounding normal skin. The size of lesions was assessed by observing their margins. The results were labeled as excellent, good, moderate and poor. All the findings were tabulated.

## Results

In group 'A', there were 5 males and 19 females, while group 'B' comprised 7 males and 17 females. **Table 1** reveals the results at the completion of study. Significant clinical improvement i.e. excellent and good response, was observed in both the groups by the end of 6 months therapy i.e. group 'A' 17 patients (71%,  $p < 0.05$ ) and group 'B' 19 patients (79%,  $p < 0.05$ ). In group 'A', clinical improvement was observed by the end of 9<sup>th</sup> week of therapy while group 'B' subjects responded earlier i.e. by the 6<sup>th</sup> week. Maximum response was seen by the end of 3 months therapy in both groups. In group 'A', 7 patients (29%) had moderate or no response. Only 5 patients (21%) in group 'B', showed mild to moderate response. There was slight improvement thereafter in the second half, once the patients were switched to alternate day therapy. Therefore, significant treatment difference was not a feature by the end of 6 months therapy.

There was no systemic toxicity in any of the patients. Serious local adverse effects were not observed. Mild skin irritation of transient nature was observed in 10% of the patients. Clinical findings comprised of mild erythema, scaling, itching and stinging sensations. No residual hypochromia and leukoderma were observed. There was no complaint of post-inflammatory hyperpigmentation.

## Discussion

Azelaic acid is a saturated dicarboxylic acid,<sup>16</sup> a naturally occurring substance. It is an established therapeutic agent for the management of acne having comedolytic,<sup>17,18</sup> antibacterial<sup>19,20</sup> and anti-inflammatory<sup>21</sup> effects. Earlier, for its

**Table 1** Clinical response at the completion of therapy (n=48)

Response	Group A %	Group B %
Excellent	2 (8.5%)	8 (33%)
Good	15 (62.5%)	11 (46%)
Moderate	4 (16.5%)	3 (12.5%)
Poor	3 (12.5%)	2 (8.5%)

effect to induce hypopigmentation in tinea versicolor, it was assumed to have a direct competitive inhibition of tyrosinase, the key enzyme in melanin synthesis.<sup>22</sup> Hu *et al.*<sup>23</sup> indicated later on that this inhibitory influence is partial and indirect. He showed that azelaic acid inhibits the membrane enzyme thioredoxin reductase leading to an increased intracellular concentration of thioredoxin, which in turn is a potent inhibitor of tyrosinase. Moreover, azelaic acid also exerts inhibitory effect on the growth and viability of melanocytes.<sup>24</sup> This in turn is brought about by the inhibition of mitochondrial cellular respiration as well as DNA synthesis. The efficacy of azelaic acid is good in melasma but it is not considered superior to hydroquinone.<sup>25</sup>

Tretinoin on the other hand is a potent inhibitor of new melanin synthesis and is effective in the management of postinflammatory pigmentation as well as melasma.<sup>26-28</sup> In addition, tretinoin also exerts keratolytic effect, which in turn also inhibits pigmentation.<sup>29-31</sup>

Generally, azelaic acid is not considered superior to hydroquinone. Azelaic acid as a monotherapy is however, superior to hydroquinone 2% but inferior to hydroquinone 4%, when used in combination with a broad-spectrum sunscreen.<sup>32</sup> Azelaic acid used in combination with a broad-spectrum sunscreen has been reported to be well

tolerated with an efficacy of 65-70% in melasma.<sup>33,34</sup> In group 'A', 71% patients showed significant clinical improvement i.e. excellent (8.5%) and good (62.5%) response, while the other 29% responded moderately (16.5%) or poorly (12.5%) ( $p<0.05$ ) Therefore, the finding in our study as far as the group 'A' is concerned, is consistent with the literature.<sup>34,35</sup>

As the response to therapy in melasma is slow, multidrug regimens, e.g. azelaic acid in combination with tretinoin may be advised. Tretinoin promotes melanosome transfer and epidermal turnover leading to removal of melanin. Tretinoin (0.01%) cream as a monotherapy acts slowly.

Our results indicate that the combination therapy of azelaic acid and tretinoin is better than azelaic acid therapy alone. The net result in the group 'B' was a significant improvement in 79% of the patients ( $p<0.001$ ) in contrast to 71% ( $p<0.05$ ) in group 'A'. Moreover, a shorter time was required to produce the clinical result with the combination therapy. The lightening in color was seen by the end of 6<sup>th</sup> week of therapy in contrast to 9<sup>th</sup> week in group B. Thus, tretinoin augments the effect of azelaic acid by a synergistic mechanism. Verillo Rowell *et al.*<sup>35</sup> have already confirmed the clinical efficacy of azelaic acid cream (20%) used in combination with tretinoin and a broad-spectrum sunscreen. Therefore, the combination regimen of tretinoin and azelaic acid is superior to when either is used as a monotherapy. Zaumseil *et al.*<sup>36</sup> have reported the success of a similar combination therapy. Thus, the results of our open comparative trial are in accordance with previous studies.

Regarding the tolerability of these therapies, there was no systemic toxicity in any of the patients. No serious local adverse effects were observed. Mild skin irritation of transient nature was observed in 10% of the patients. Clinical findings comprised of mild erythema, scaling, itching and stinging sensations.

## Conclusion

It can be concluded from the above study that azelaic acid when used in combination with tretinoin is more effective than azelaic acid monotherapy. The combination induces lightening of skin color in a shorter time interval.

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