ORIGINAL ARTICLE

A comparative study of 20% azelaic acid cream versus 5% tranexamic acid solution for the treatment of postinflammatory hyperpigmentation in patients with acne vulgaris: A single-blinded randomized clinical trial

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Background: There is a lack of evidence on the therapeutic efficacy of topical tranexamic acid (TA) for the treatment of acne-related postinflammatory hyperpigmentation (PIH). The current study aimed to assess the efficacy of twice-daily administration of 20% azelaic acid (AZA) cream versus 5% TA solution for the treatment of PIH in patients with acne vulgaris. **Materials and Methods:** Patients in the present single-blinded randomized clinical trial were randomized into AZA or TA groups for 12 weeks. The rate of healing was assessed by scoring recorded photographs based on postacne hyperpigmentation index (PAHI) at baseline, 4th, 8th, and 12th weeks. The frequency of side effects was examined and recorded at each study time point. **Results:** Thirty volunteers in each treatment group completed the intervention. PAHI score in both AZA and TA groups improved during the study course ($P_{time} < 0.001$, for both groups). However, mean PAHI scores were comparable in the two groups ($P_{group} = 0.05$). No significant interaction was also found between time and treatments in terms of PAHI score ($P_{time \times group} = 0.66$). The frequency of treatment-related side effects was significantly higher in the AZA group compared to the TA group at week 4 of treatment ($P < 0.05$). However, no significant difference was observed in the frequency of reported side effects at weeks 8 and 12 of the treatment ($P > 0.05$). **Conclusion:** Topical administration of 20% AZA cream and 5% TA solution was comparably efficient in the treatment of acne-related PIH with a significantly better safety profile of TA in the 1st month of the treatment.

Key words: Acne vulgaris, azelaic acid, postinflammatory hyperpigmentation, tranexamic acid

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INTRODUCTION

Postinflammatory hyperpigmentation (PIH) is a prevalent sequela of various cutaneous inflammations, which adversely impacts individuals' quality of life.[1] PIH appears as asymptomatic, hyper-pigmented macules or patches located in the area of former cutaneous inflammations.[2] It develops by a wide range of inflammatory predictors such as dermatologic procedures, extrinsic factors (e.g., burns and injuries), and dermatoses.[3] Acne vulgaris is one of the most common causes of PIH, particularly in people with Fitzpatrick skin types III–VI.[4]

Various treatment options have been proposed for the treatment of PIH comprising topical agents, chemical peels (e.g., salicylic acid and glycolic acid), and laser therapy. Topical hydroquinone (2% to 4%) alone or in

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combination with other agents is an efficient conventional treatment option for hyperpigmentation disorders of the skin. Although long-term topical application of hydroquinone is limited due to the risk of ochronosis which has been reported both in high- and low-hydroquinone concentrations.[5] Thus, nonhydroquinone topical agents with better safety profiles were noticed for the treatment of hyperpigmentation disorders.

Azelaic acid (AZA), a dicarboxylic acid derived from pityrosporum ovale, acts as a depigmentation topical agent by affecting heavily pigmented melanocytes. Several previous studies have examined the efficacy of AZA in the treatment of skin hyperpigmentation disorders in comparison to hydroquinone. The results of these studies have revealed that AZA is more beneficial than hydroquinone for hyperpigmentation treatment.[6,7] A double-blind comparative study of 155 patients with melasma indicated that lesions size and pigmentary intensity decreased in 73% of individuals treated with twice-daily 20% AZA compared to 19% of individuals treated with 2% hydroquinone after 24 weeks of treatment.[6] Furthermore, another study by Farshi reported that across a treatment period of 8 weeks, twice-daily application of 20% AZA was more effective than 4% hydroquinone for the treatment of mild melasma.[7] Nevertheless, the poor aqueous solubility and skin penetrability of AZA results in its formulation at higher doses (10%–20%) to achieve a satisfactory therapeutic effect. This may limit AZA therapeutic applicability due to dose-dependent side effects such as erythema, dryness, burning, scaling, and peeling.[8]

Tranexamic acid (TA), trans-4-aminomethyl cyclohexane carboxylic acid, is known to have depigmentation properties in various forms comprising topical, oral, and localized intradermal microinjection. In recent years, topical TA has received much attention as either monotherapy or adjuvant treatment for skin hyperpigmentation diseases.[9-12] The results of comparative studies have shown that topical TA is as efficacious as hydroquinone in the treatment of hyperpigmentation disorders such as melasma.[13,14] In addition, it has been demonstrated that the systemic and intradermal administration of TA is beneficial for PIH treatment.[15,16] However, to the best of our knowledge, no previous study has examined the effect of topical TA on acne-related PIH. Therefore, the present study aimed to investigate the efficacy and safety of 5% TA solution versus 20% AZA cream for PIH treatment in patients with acne.

MATERIALS AND METHODS

Patients and study design

This single-blinded, randomized clinical trial was conducted from May 2019 to May 2021 in the dermatology clinic of Sina hospital, affiliated with Hamadan University of Medical Sciences (HUMS), Hamadan, Iran. The required sample size was estimated to be 30 in each treatment group considering, power 80%, type I error 0.05, for detecting a standardized effect size of 0.8 in PIH.[17] Volunteers were included in the present study if they were 18–45 years old, had at least one dermatologist-diagnosed acne-related PIH, and did not use any anti-hyperpigmentation agents such as hydroquinone and its derivatives, glutathione, cysteamine, Vitamin C, Kojic acid, arbutin, and tretinoin during the previous 3 months were recruited for the study. The exclusion criteria included pregnancy, lactation, history of AZA and TA allergy, the use of oral contraceptive and photosensitizing agents, history of color vision impairment, or disorders that increase the risk of thromboembolic events such as deep-vein thrombosis, myocardial infarction, cerebral stroke, and chronic kidney disease. At baseline, eligible participants were clinically assessed and their baseline characteristics comprising age, sex, educational status, Fitzpatrick skin phototype, affected body regions; disease duration, previous treatment history, and its duration were recorded.

The protocol of the study complied with the guidelines of the Declaration of Helsinki and was approved by the ethics committee of HUMS (Research number: IR.UMSHA.REC.1399.150). The study protocol was also registered in the Iranian Registry of Clinical Trials under the registration number IRCT20120215009014N356. Participants were informed about the study objectives and a written informed consent form was obtained from each of them before recruitment.

Randomization, blinding, and treatment procedure

Participants who met the inclusion criteria were randomized to 20% AZA cream (Sepidaj pharmaceutical company, Tehran, Iran) or 5% TA solution (diluted solution of TA 500 mg/5 ml (Caspian Tamin pharmaceutical company, Gilan, Iran). The randomization was performed by a third independent blinded researcher using a simple randomization design generated from the website of www.randomization.com. The assigned treatment agents were applied twice daily (one time in the morning and one time at night before bedtime) for 12 weeks in both groups. Participants were instructed to use assigned topical agents on acne-related PIH lesions after washing their faces thoroughly with bland soap and water and patting them dry. Patients were asked to apply a sunscreen cream (with a sun protection factor of 30) for half an hour after using AZA cream and TA solution in the morning. In addition, participants were prohibited to use any cosmetics or undergo any therapeutical facial procedure during the treatment period.

Outcomes evaluation

The primary endpoint of the study was the rate of healing in acne-related PIH assessed by two dermatologists

who scored recorded photographs based on postacne hyperpigmentation index (PAHI) at baseline, 4th, 8th, and 12th weeks. As shown in Table 1, PAHI is the summation of three scores comprising the number of lesions, median lesion size, and median lesion intensity with a total score ranging from 6 to 22 with the greater score indicating a more severe condition. Secondary endpoints were patients' treatment satisfaction scores and treatment-related side effects. Patients were asked to determine their satisfaction with the treatment based on a 10-point Visual Analog Scale, where 0 indicated no satisfaction and 10 indicated the highest satisfaction. Side effects including pain, itching, erythema, and blisters were assessed and recorded in each follow-up visit.

Statistical analysis

All statistical analyses were performed by Statistical Package for the Social Sciences (SPSS, Inc., Chicago IL, USA; version 26). Quantitative data were expressed as mean ± standard deviation; however, qualitative data were presented by frequency (percentage). Normality was evaluated using the Kolmogorov–Smirnov test and Q–Q plot. Student's *t*-test and Chi-squared test were used for comparing basic continuous and categorical characteristics of study participants between two groups. Repeated measures analysis of variance was used for evaluating a between-group differences in terms of main study outcomes followed by contrast analysis for comparing the mean values of study outcomes at each time follow-up with baseline. The sphericity assumption was evaluated by Mauchly's test and when it was violated the multivariate approach was adopted. The mean changes from baseline for each time point were computed and compared between two groups by independent samples *t*-test. We also used the Chi-squared test for comparing the frequency of side effects between two groups at each time point. $P < 0.05$ were considered statistically significant.

RESULTS

In total, 90 patients were screened for eligibility. Of those, eight patients did not meet the inclusion criteria; thus, 82 patients were randomized in the AZA (n = 41) and TA (n = 41) groups. In the TA group, 11 individuals refused to continue the treatment due to withdrawal from cooperation. Moreover, 11 patients in the AZA group discontinued the study due to side effects. Finally, 30 patients in each group completed the study [Figure 1].

The basic characteristics of the participants are summarized in Table 2. Our results indicated that there was no significant difference between the two groups regarding age, sex, Fitzpatrick skin phototype, affected body regions, disease duration, history, and duration of previous treatment ($P > 0.05$).

Table 1: Postacne hyperpigmentation index

Weighed score	Median lesion size
2	<3
4	3-6
6	7-10
8	>10
Weighed score	**Median lesion intensity**
3	Slightly darker than surrounding skin
6	Moderately darker than surrounding skin
9	Significantly darker than surrounding skin
Weighed score	**Number of lesions**
1	1-15
2	16-30
3	31-45
4	46-60
5	>60

Table 2: Comparing basic characteristics of participants in azelaic acid and tranexamic acid treatment groups

	AZA, *n* (%)	TA, *n* (%)	*P*
Age (years)	24.4±47.97	25.5±86.84	0.404
Sex			
Males	15 (50.0)	8 (26.7)	0.063
Females	15 (50.0)	22 (73.3)	
Fitzpatrick skin phototype			
II	11 (50.0)	15 (36.7)	0.626
III	16 (43.3)	13 (53.3)	
IV	3 (6.7)	2 (10.0)	
Duration of disease (years)			
≥2	12 (40.0)	19 (63.3)	0.401
>2	18 (60.0)	11 (36.7)	
Affected body regions			
Face	22 (73.3)	22 (73.3)	0.336
Trunk	2 (6.7)	5 (16.7)	
Limbs	6 (20.0)	3 (10.0)	
Previous treatment			
Yes	12 (40)	19 (63.3)	0.071
No	18 (60)	11 (36.7)	
Duration of previous treatment (months)			
≥1	3 (25.0)	7 (36.8)	0.216
1-6	8 (66.7)	8 (42.1)	
6-12	1 (8.3)	4 (21.1)	

P<0.05 is considered significant. Values in the table are mean±SD for continuous variables and *n* (%) for categorical variables, *P* values are obtained from independent samples *t*-test for continuous variables, and Chi-square test for categorical ones. SD=Standard deviation; TA=Tranexamic acid; AZA=Azelaic acid

The mean PAHI score at each study time point in the AZA and TA groups is presented in Figure 2 and Table 3. PAHI score was improved during the study course in both AZA and TA groups ($P_{time} < 0.001$, for both groups) [Figure 2 and Table 3]. The mean PAHI scores were comparable in two groups at baseline (10.47 ± 3.86 vs. 12.10 ± 3.15) as well as weeks 4 (9.23 ± 3.17 vs. 10.43 ± 2.70), 8 (7.63 ± 1.73 vs. 8.80 ± 2.45), and 12 (7.00 ± 1.63 vs. 7.80 ± 2.19) ($P_{group} = 0.05$). No significant interaction

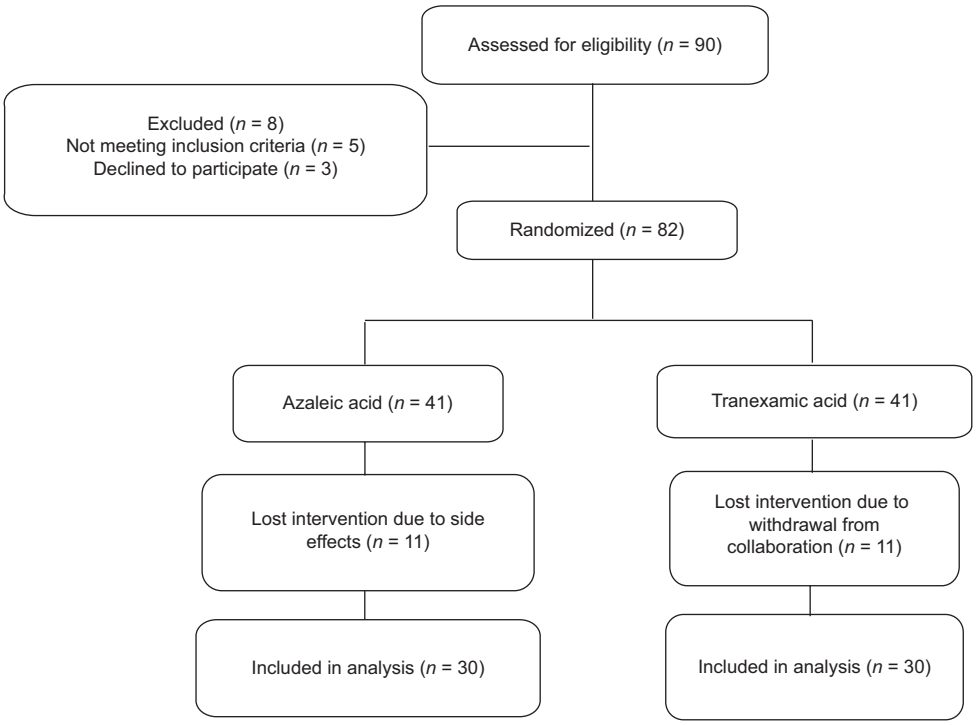

Figure 1: Flowchart for selection of study participants

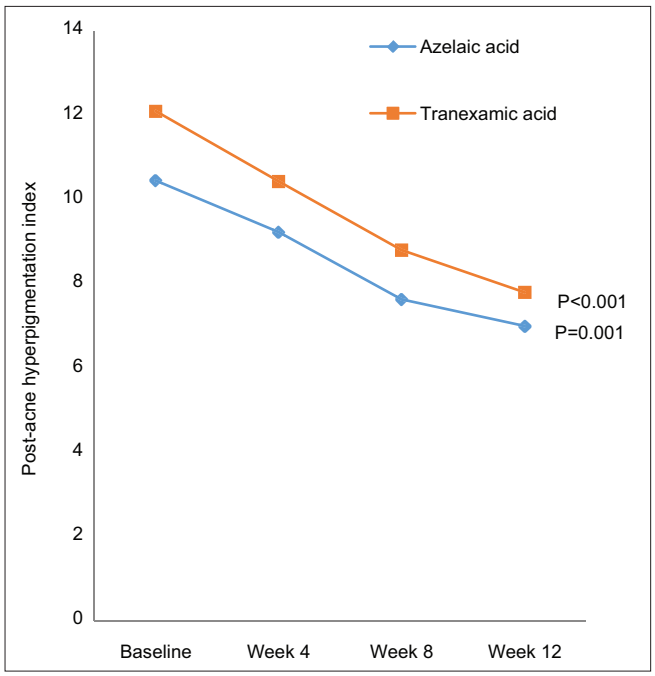

Figure 2: Mean of PAHI in azelaic acid and tranexamic acid treatment groups in each study time point. PAHI = Postacne hyperpigmentation index P values resulted from repeated measure ANOVA, $P < 0.05$ is considered statistically significant. ANOVA = Analysis of variance

was also found between time and treatments on PAHI score ($P_{time \times group} = 0.66$) [Table 3].

Patients' treatment satisfaction in both treatment groups of AZA ($P_{time} = 0.01$) and TA ($P_{time} < 0.001$) improved at the end of the follow-up time. However, the mean patients' treatment satisfaction scores were comparable in two groups at weeks 4 (6.90 ± 1.95 vs. 7.10 ± 1.86), 8 (7.33 ± 1.75 vs. 7.77 ± 1.87), and 12 (7.53 ± 1.72 vs. 8.13 ± 1.65) ($P_{group} = 0.36$). In addition, no significant time × group interaction on patients' treatment satisfaction was observed ($P_{time \times group} = 0.30$) [Table 3].

Table 3: Comparing means of postacne hyperpigmentation index and treatment satisfaction scores between azelaic acid and tranexamic acid treatment groups in each study time point

	Mean±SD		*P*	P_{group}	$P_{time \times group}$
	AZA	TA			
PAHI					
Baseline	10.47±3.86	12.10±3.15	0.078	0.05	0.66
Week 4	9.23±3.17	10.43±2.70	0.120		
Week 8	7.63±1.73	8.80±2.45	0.064		
Week 12	7.00±1.63	7.80±2.19	0.069		
P_{time}	<0.001	<0.001			
Treatment satisfaction score					
Week 4	6.90±1.95	7.10±1.86	0.686	0.36	0.30
Week 8	7.33±1.75	7.77±1.87	0.358		
Week 12	7.53±1.72	8.13±1.65	0.150		
P_{time}	0.01	<0.001			

P<0.05 is considered statistically significant. *P* values resulted from repeated measure ANOVA. PAHI=Postacne hyperpigmentation index; TA=Tranexamic acid; AZA=Azelaic acid; SD=Standard deviation

A significant reduction was observed in the mean difference of PAHI score at weeks 4 (mean difference ± SE: −1.24 ± 0.36), 8 (mean difference ± SE: −2.84 ± 0.54), and 12 (mean difference ± SE: −3.47 ± 0.59) from baseline in the

AZA group ($P < 0.05$) [Figure 3 and Table 4]. Identically, a significant reduction was found in the mean difference of PAHI score at weeks 4 (mean difference ± SE: −1.67 ± 0.37), 8 (mean difference ± SE: −3.30 ± 0.40), and 12 (mean difference ± SE: −4.30 ± 0.43) from baseline in the TA group ($P < 0.05$) [Figure 4 and Table 4]. However, the change in mean PAHI score at weeks 4, 8, and 12 of treatment from baseline was not statistically significant between AZA and TA groups ($P > 0.05$). In addition, a significant increase was observed in the mean patients' treatment satisfaction scores at weeks 8 and 12 compared to week 4 of treatment in AZA and TA groups ($P < 0.05$). While no significant difference was found between the two groups regarding mean differences in patients' treatment satisfaction scores [Table 4].

After 4 weeks of treatment, a significant difference was noted in the frequency of treatment-related side effects between AZA and TA groups (36.6% vs. 3.3%) ($P < 0.05$). As, only one individual (3.3%) in the TA group reported erythema; however, in the AZA group, erythema and burning were reported by 7 (23.3%) and 4 (13.3%) individuals, respectively. No severe side effect was reported after 8 and 12 weeks of treatment in the TA group. However, 10% of individuals in the AZA group reported erythema at weeks 8 and 12 of treatment. However, no significant difference was noted between the two groups regarding reported side effects after 8 and 12 weeks of treatment ($P > 0.05$) [Table 5].

DISSCUSION

PIH is a common skin condition with a significant psychological burden that can occur as a result of various dermatoses such as acne vulgaris.[18] The acne-related cutaneous inflammation stimulates hypermelanosis in

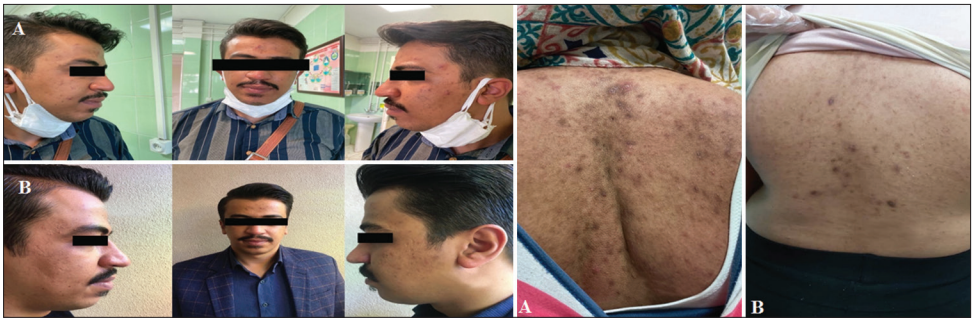

Figure 3: Two patients in the azelaic acid group before treatment (A) and after 12 weeks of treatment (B)

Figure 4: Two patients in the tranexamic acid group before treatment (A) and after 12 weeks of treatment (B)

Table 4: The comparison of changes in the mean of postacne hyperpigmentation index and treatment satisfaction scores between azelaic acid and tranexamic acid treatment groups

	AZA (mean±SE)	P_1	TA (mean±SE)	P_1	P_2
PAHI					
Week 4-baseline	−1.24±0.36	0.011	−1.67±0.37	0.001	0.868
Week 8-baseline	−2.84±0.54	<0.001	−3.30±0.40	<0.001	0.238
Week 12-baseline	−3.4±70.59	<0.001	−4.30±0.43	<0.001	0.472
Treatment satisfaction score					
Week 8–week 4	0.43±0.16	0.029	0.67±0.12	<0.001	0.175
Week 12–week 4	0.63±0.19	0.009	1.03±0.16	<0.001	0.052

$P<0.05$ is considered significant. P_1 resulted from contrast analysis followed by repeated measures ANOVA, and P_2 resulted from Independent samples *t*-test or Mann-Whitney *U*-test. PAHI=Postacne hyperpigmentation index; TA=Tranexamic acid; AZA=Azelaic acid; SE=Standard error

Table 5: Comparing the frequency of treatment-related side effects in azelaic acid and tranexamic acid treatment groups in each study time points

	AZA, *n* (%)	TA, *n* (%)	*P*
Week 4			
No side effects	19 (63.3)	29 (96.7)	0.003
Erythema	7 (23.3)	1 (3.3)	
Burning	4 (13.3)	0	
Week 8			
No side effects	27 (90.0)	30 (100.0)	0.237
Erythema	3 (10.0)	0	
Burning	0	0	
Week 12			
No side effects	27 (90.0)	30 (100.0)	0.237
Erythema	3 (10.0)	0	
Burning	0	0	

P<0.05 is considered significant. *P* values resulted from Fisher's exact test.
TA=Tranexamic acid; AZA=Azelaic acid

the epidermis and dermis, particularly in individuals with Fitzpatrick skin types III–VI.[19] To date, there is little robust evidence available on efficient therapeutic options for the treatment and management of this condition. The present study aimed to compare the efficacy of 20% AZA cream versus 5% TA solution in the treatment of acne-related PIH.

Our results indicated that the PAHI score significantly improved during 12 weeks of treatment in the AZA group. Similarly, the findings of a baseline-controlled pilot study indicated that twice-daily administration of AZA gel 15% was effective in the treatment of moderate-to-severe acne-related PIH. According to the results of the study, complete remission of PIH was observed in 31% of patients after topical application of AZA gel.[20] Lowe *et al*. in a randomized, double-blinded, vehicle-controlled study of 52 patients of darker-skinned patients (Fitzpatrick skin types IV–VI) with facial hyperpigmentation reported that topical application of 20% AZA was associated with a significant reduction in pigmentary intensity, measured by the investigator's subjective scale and chromameter analysis. However, not all cases of hyperpigmentation in this study were acne-related.[21] It has been suggested that AZA maybe exert cytotoxic effects on melanocytes by inhibiting mitochondrial enzymes and DNA synthesis.[22] Further large-scale population-based studies are required to investigate the effect of topical AZA on acne-related PIH in various skin types.

In recent years, TA has been known as a novel therapeutic agent for hyperpigmentation treatment. Previous literature has reported that systemic and intradermal TA, alone or as adjuvant treatment options, are effective in the treatment of PIH.[15,16,23,24] However, we could not find any evidence of the efficacy of topical TA on PIH. The role of topical TA in the treatment of other hyperpigmentation disorders such as melasma has been reported by a few studies with inconclusive results.[9-12] The results of a prospective study by Kim *et al*. indicated that topical application of 2% TA resulted in a significant clinical improvement in patients with melasma.[9] However, Kanechorn *et al*. in a double-blind, randomized prospective study reported that topical 5% TA could not improve pigmentation in melasma patients with darker skin types.[10] In addition, the beneficial effect of topical TA in the treatment of melasma in combination with niacinamide and microneedling was demonstrated previously.[11,12] Although its underlying mechanisms of action are not fully understood, it has been hypothesized that TA prevents the conversion of plasminogen to plasmin by blockade of its lysine-binding sites. The inhibitory function of TA on plasmin formation results in reduced production of free arachidonic acid and prostaglandins and consequent reduction in melanocyte tyrosinase activity.[25]

According to our findings, no significant difference was observed between AZA and TA groups in terms of PAHI score. Assessing the side effects of AZA and TA treatments showed a significant between-group difference between the two groups at week 4. As a result, our findings suggest that TA is as effective as AZA in the treatment of acne-related PIH with a better side effect profile, particularly during the 1 month of the treatment. The effectiveness of 20% AZA has been compared to topical 3% TA in combination with oral TA, in 100 participants with melasma for 6 months in a study by Malik *et al*. The results of the study indicated that the mean score of the Melasma Area and Severity Index was significantly lower in the TA group in comparison to the AZA group.[26] It is postulated that the cotreatment with oral and topical TA may be more effective for hyperpigmentation. Although further studies are needed to confirm this hypothesis.

This study has several limitations. First, a small sample size from a single dermatology center was assessed, which limits the generalizability of our results. However, to the best of our knowledge, this is the first clinical trial that has evaluated the efficacy of TA in comparison with AZA in the treatment of acne-related PIH. As a result, further large-scale randomized clinical trials are required to confirm the preliminary findings of the present study.

CONCLUSION

The results of the present study showed that topical administration of 20% AZA and 5% TA is efficient in the treatment of PIH in patients with acne vulgaris. However, TA may be safer than AZA. Further studies are needed to confirm the generalizability of these findings.

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Conflicts of interest

There are no conflicts of interest.

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