COMPARISON BETWEEN TOPICAL APPLICATION OF TRANEXAMIC ACID AND ERYTHROMYCIN IN THE TREATMENT OF ROSACEA

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ABSTRACT

Background

Rosacea is a common, chronic relapsing disease, characterized by erythema, telangiectasias, inflammatory papule, and pustule mainly on the mid-face for which many therapies may exist but with limited efficacy. Tranexamic acid is an anti-fibrinolytic drug that acts by inhibiting the action of plasmin and is mainly used to reduce bleeding. Erythromycin is one of the macrolide antibiotics that acts by inhibiting bacterial protein synthesis and in addition to this action it has an immune modulatory effect.

Objectives

To evaluate the effects of tranexamic acid solution in the treatment of rosacea and compare it with erythromycin gel.

Methods

In this study, thirty (30) patients were included, twenty-three patients were women and 7 of them were men, their ages ranged between 28-50 years old with signs and symptoms of rosacea. The patients were grouped into 2 groups; the first group was treated with a derma pen simultaneously with a tranexamic acid solution (Transamin inj/sol 500 mg/5ml) topical application followed by infused wet dressing for 15 minutes, every 7 days for five (5) sessions. The second group was treated with erythromycin gel twice daily for 5 weeks.

Results

At the end of the study all the patients were improved, the improvement was outlined according to the investigator Global Assessment of Rosacea Severity Score (IGA-RSS) and the use of clinical photos. There was a statistically significant improvement (2) units IGA-RSS for tranexamic acid group and (2,8) units for erythromycin gel.

Conclusion

A tranexamic acid solution is a safe, simple, and cheap treatment option for rosacea. It is also as effective as an erythromycin antibiotics to relieve the symptoms of rosacea.

Keywords: *Tranexamic acid; Rosacea; Erythromycin.*

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INTRODUCTION

Rosacea is a common inflammatory facial disorder. The common manifestations of rosacea include recurrent erythema, telangiectasia, inflammatory papules and pustules on the mid-face, or rhinophyma in severe cases [1]. Telangiectasia and redness are among the most common visible signs of rosacea in patients presenting to dermatology practices [2]. These features frequently become a psychological burden and can substantially impact patients' quality of life and self-esteem [3]. Females and males are affected equally [4]. Persons with fair skin type have an increased risk of rosacea [5]. The pathophysiology is not completely understood, but dysregulation of the immune system, as well as changes in the nervous and the vascular system, have been identified.

Recent studies have suggested that protease-activated receptor 2 (PAR-2) could be involved in the pathogenesis of rosacea, PAR-2 is a G-protein-coupled 7-transmembrane domain receptor, which mediates inflammation in various tissues upon activation by serine proteases (SPs) such as kallikrein [6,7]. Microbes that are part of the normal skin flora, and specifically in the pilosebaceous unit – including Demodex mites and *Staphylococcus epidermidis* – may also play a role as triggers of rosacea [8,9]. The current therapies for rosacea have certain limitations, and prevention of relapse requires long-term maintenance therapy [1].

Trans-4-(Aminomethyl) cyclohexane carboxylic acid, or tranexamic acid (TXA), a synthetic lysine derivative that blocks the lysine site on plasminogen and inhibits fibrinolysis, was first described in 1966. Its first application demonstrated a reduction of menstrual bleeding in 1968. The use of TXA to reduce bleeding was described in many surgical and medical settings [10]. Recently, (TXA), has been proposed as a new treatment for melasma. In 1979, Nijo Sadako accidentally discovered its effect during the treatment of a patient with chronic urticarial [11].

Erythromycin is one of the macrolide group antibiotics, it was first isolated in 1952 from the bacteria Saccharopolyspora erythraea. It is an antibiotic used for the treatment of some bacterial infections. This includes respiratory tract infections, skin infections, chlamydia infections, pelvic inflammatory disease, and syphilis. Common side effects include abdominal cramps, vomiting, and diarrhea [12].

Erythromycin is used in papulopustular rosacea, its effectiveness at sub-antimicrobial doses is mostly due to their anti-inflammatory properties rather than a direct antimicrobial mechanism. Although bacteria may contribute to this form of rosacea, evidence for this is scant [9, 13, 14].

In the present study, we decided to test the efficacy of topical applications of tranexamic acid in patients of rosacea and compare it to those patients using topical erythromycin in the treatment of rosacea.

METHODS

A randomized, open-label study was conducted after the protocol has been read and approved by the Ethical Committee of Sulaimani University, College of Medicine, Kurdistan region, Iraq. Informed consent was obtained from all patients before the study. After obtaining detailed personal and medical history "Thirty patients" aged 28-50 years, were enrolled in this study, most of the patients were women (23) and the rest were men, the patients were recruited according to the diagnostic criteria of rosacea [1]. The following were the exclusion criteria for the study: facial acne, dermatitis, recent drug treatment like steroids or antibiotics for the last 4 weeks, pregnancy, lactation, and systemic diseases that affect the skin assessment.

The thirty participants were grouped randomly into two groups, for the first group (15) patients: We explained the procedure to the patients and after cleaning the face, topical Emla cream 5% (lidocaine 25mg/g and prilocaine 25mg/g), was applied to the area of rosacea for about half an hour, after that the area was treated with derma pen simultaneously with a tranexamic acid solution (transmit inj/sol 500 mg/5ml) topical application followed by tranexamic acid solution infused wet dressing therapy every 7 days for five sessions.

After completion of the session the patients were advised to avoid excessive sun exposure, apply a broad-spectrum sunscreen with a sun protection factor of SPF 50 in the morning, and reapply the sunscreen every 2 hours, avoid skin irritation, Skincare should include a gentle facial cleanser and a moisturizer, Avoiding triggers such as extreme temperatures (hot or cold), spicy foods, hot or alcoholic beverages, wind, exercise and stress and also avoiding medications that might worsen rosacea or trigger flushing episodes. These include calcium channel blockers, nitrates, nicotinic

acid, and some vitamin B-related medications including niacin[15].

For the second group, we asked them to use the ordinary treatment of rosacea which was erythromycin gel (eryacne gel 4%) twice daily for 5 weeks.

The results were evaluated statistically by using the Statistical Package for the Social Sciences (SPSS) version 26.0. The Shapiro-Wilk test was used to determine the normal distribution of the data. An independent t-test was used to compare the results. A Chi-square test of association was used to compare between proportions. When the expected count of more than 20% of the cells of the table was less than 5, Fisher's exact test was used. Differences between the mean and standard deviation of the scores were statistically analyzed using the Friedman test, while the Wilcoxon test was used to compare individual pairs of groups. Changes were considered statistically significant when the P-value was 0.05 or less

RESULTS

From January 2019 to January 2020, 23 women and 7 men with rosacea were included in this study. The characteristics of 30 patients are summarized in Table 1.

The mean IGA-RS score (mean + standard deviation) of all participants (tranexamic acid and erythromycin) at the baseline time are shown in Table 2. The mean IGA-RS score of the baseline in the TA group was 4.2 ± 1.3, while in the erythromycin group was 4.4 ± 1.4.

The mean IGA-RS score (mean + standard deviation) of the baseline and all reassessment visits after treatment with TA are shown in Table 3. The mean IGA-RS score of the baseline was 4.4 ± 1.24 while after 5 weeks it reached 2 ± 0.53 (P=0.001) (Figure 1,2).

The mean IGA-RS score (mean + standard deviation) of the baseline and reassessment visits after treatment with erythromycin are shown in Table 4. The mean IGA-RS score of the baseline was 4.26 ± 1.33 while after 5 weeks it reached 2.86 ± 1.3 (P=0.02) (Figure 3).

The mean IGA-RS score of the TA and erythromycin groups after 5 weeks of treatment are shown in Table 5. The mean IGA-RS score of the TA was (2.86 ± 1.3). Furthermore, in erythromycin was (2.8 ± 0.53) (P = 0.02).

Table 1. The characteristic of the participants.

	Tranexamic acid		Erythromycin		P value
Age	36.5 ± 6.2		37.5 ± 6.3		0.64
Gender	Men	Women	Men	Women	0.002
	0 (%0)	15 (100%)	8	7	
Systemic diseases	No	Yes	No	Yes	0.99
	11 (73.3%)	4 (26.7%)	10 (66.7%)	5 (33.3)	
Drug History	NO	Yes	NO	Yes	0.99
	11 (73.3%)	4 (26.7%)	10 (66.7%)	5 (33.3)	
Smoking	No	Yes	No	Yes	0.71
	8 (53.3%)	7 (46.7%)	10 (66/7%)	5 (33.3%)	
Family History	No	Yes	No	Yes	0.245
	8 (53.3%)	7 (46.7%)	12 (80%)	3 (20%)	

Table 2. The mean IGA-RS score (mean ± SD) of the participants, at the baseline t ime of tranexamic acid and erythromycin groups.

Variables	Tranexamic acid Baseline			Erythromycin Baseline			P value
Severity	Mild	Moderate	Sever	Mild	Moderate	Sever	
	1 (6.7%)	6 (40%)	8 (53.3%)	2 (13/3%)	6 (40%)	7 (46/7%)	0.82
Score		4.2 ± 1.3			4.4 ± 1.4		0.44

IGA-RSS= Investigator Global Assessment of Rosacea Severity Score
IGA-RSS 1,2= mild
IGA-RSS 3,4= moderate
IGA-RSS 5,6= sever

Table 3. The mean IGA-RS score (mean ± SD) of Tranexamic acid at the baseline and after 5 weeks of treatment with Tranexamic acid (transmit inj/sol 500 mg/5ml).

Variables	Tranexamic acid Baseline			Tranexamic acid After 5 weeks			P value
Severity	Mild	Moderate	Sever	Mild	Moderate	Sever	
	1 (6.7%)	6 (40%)	8 (53.3%)	13 (86.7%)	2 (13.3%)	0	0.001
Score		4.4 ± 1.24			2 ± 0.53		0.001

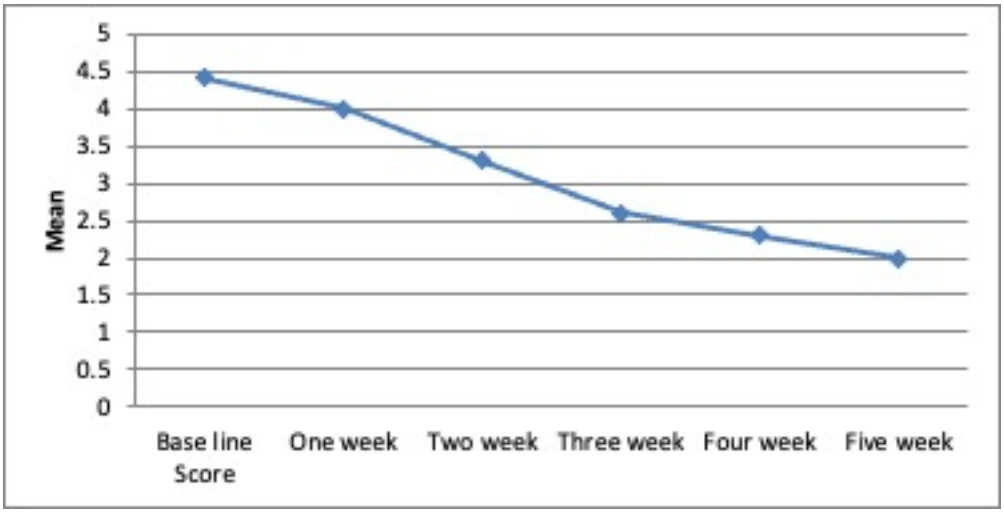

Figure 1. The mean IGA-RS score (mean ± SD) of TA at each week of visits.

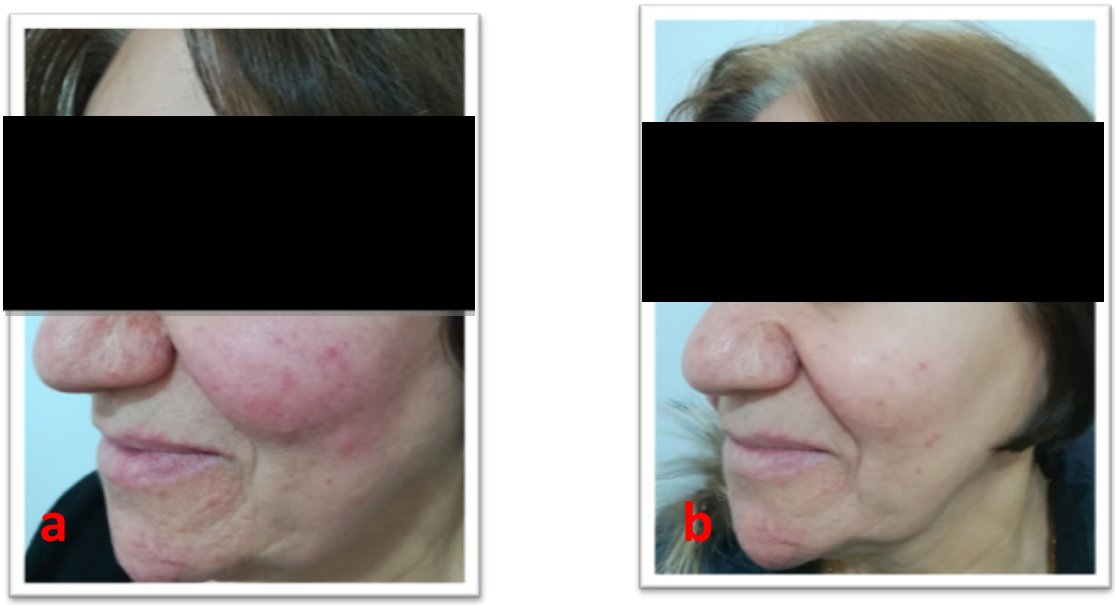

Figure 2. The face of the patient treated with tranexamic acid (a: at baseline, b: after 5 weeks)

Table 4. The mean IGA-RS score (mean ± SD) of erythromycin at the baseline and after 5 weeks of treatment with erythromycin.

Variables	Erythromycin Baseline			Erythromycin After five weeks			P value
Severity	Mild	Moderate	Sever	Mild	Moderate	Sever	0.062
	2 (13.3%)	6 (40%)	7 (46.7%)	7 (47.7%)	6 (40%)	2 (13.3%)	
Score	4.26 ± 1.33			2.86 ± 1.3			0.02

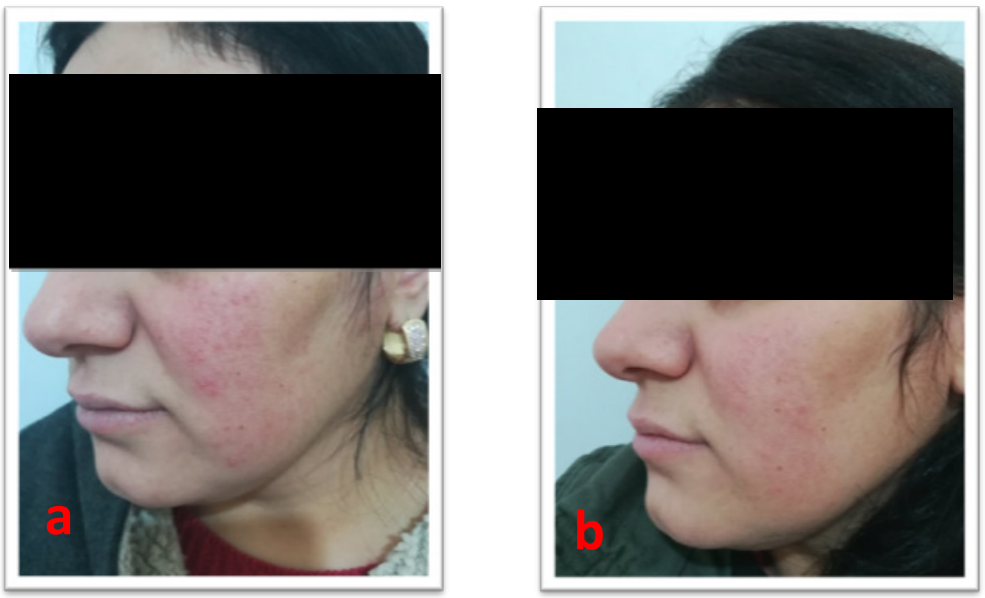

Figure 3 . The face of the patient treated with erythromycin (a: at baseline, b: after 5 weeks).

Table 5. The mean IGA-RS score of the TA and erythromycin groups after 5 weeks of treatment.

Variables	Erythromycin After 5 weeks			Tranexamic acid After 5 weeks			P value
Severity	Mild	Moderate	Sever	Mild	Moderate	Sever	0.055
	7 (46.7%)	6 (40%)	2 (13.3)	13 (86.7%)	2 (13.3%)	0 (0)	
Score	2.8 ± 0.53			2.86 ± 1.3			0.02

DISCUSSION

Rosacea is one of the common chronic inflammatory skin disorders, characterized by recurrent erythema, telangiectasia, inflammatory papules and pustules on the mid-face, or rhinophyma in severe cases [1]. The prevalence of rosacea across the populations has been reported to range from less than 1% to 22% [14]. The condition usually starts in affected persons when they are between 30 and 50 years of age and is characterized by episodes of exacerbation and remission [5]. The red, pimply facial rash can cause embarrassment, low self-esteem, and anxiety and may lead to feelings of depression and stigmatization, with a marked negative effect on the quality of life [15-17].

The diagnosis of rosacea is based on clinical features and careful history taking. A skin-biopsy specimen is obtained only to rule out other diagnoses since the histopathological features of rosacea are typically not specific to rosacea [18]. The differential diagnosis includes seborrheic dermatitis, flushing disorders, acne vulgaris, perioral dermatitis, lupus erythematosus, and chronic actinic damage [5, 19]. The pathogenesis of rosacea is unknown. However, studies suggest that disruption of epidermal permeability could play a major role in the development of rosacea [20]. It has been found that disruption of the epidermal permeability barrier enhances cytokine expression, infiltration of inflammatory cells, and expression of vascular growth factors [21]. Lee SE et al demonstrated that rosacea exhibit a high level of serine proteases (SPs) activity, which in turn activates protease-activated receptor 2 (PAR-2), and (PAR-2) signaling the influx of calcium ions in the keratinocytes of stratum granulosum which inhibit lamellar body secretion, and this is the mechanisms that (PAR-2) is involved in the regulation of permeability barrier homeostasis [22].

Management of rosacea usually starts with educating patients about the skin condition and potential exacerbating factors to help patients identify triggers and improve their coping mechanisms [5, 13, 23]. Given the impairment of the skin barrier function, irritant cosmetic products should be avoided. Ultraviolet light is a well-known trigger for rosacea; therefore, the daily use of sunscreens is recommended [5, 13, 24].

The treatment of rosacea has been a big challenge for both patients and clinicians, mainly due to the lack of approaches targeting pathogenic pathways. Treatment of rosacea includes Treatments for Flushing, Erythema, Telangiectasia, Treatments for Inflammatory Lesions, Treatments for Phyma, and Treatments for Ocular Rosacea [5, 23]. Because Rosacea is a chronic condition, and although patients can have remissions, relapses commonly occur, Therefore, patients typically receive maintenance therapy [5, 23, 25]. In this study, we demonstrate that topical [4-(aminomethyl) cyclohexane carboxylic acid,t-AMCHA] tranexamic acid improves rosacea. The mechanisms by which tranexamic acid benefits rosacea could be due to the improvement of permeability barrier function, likely resulting from the inhibition of SP.

Inhibition of SP by tranexamic acid accelerates barrier recovery and inhibits epidermal hyperplasia induced by repeated barrier disruption [26]. In addition to that as a plasmin inhibitor, tranexamic acid suppresses plasmin-induced angiogenesis, and also inhibits neovascu-larization induced by basic fibroblast growth factor (bFGF), this could reduce erythema and vessel numbers in the rosacea lesion [27]. We found in our study tha the erythema of rosacea was also reduced by tranexamic acid, which might be caused by the antiangiogenic action of tranexamic acid.

In conclusion, topically used tranexamic acid is a safe, simple, and cheap treatment option for rosacea. It is also as effective as topical erythromycin gel to relieve the symptoms of rosacea.

REFERENCES

1. Update on medical therapies. Skin Therapy Lett 2014;19:1–4.

2. Baldwin HE. Diagnosis and treatment of rosacea: State of the art. J Drugs Dermatology 2012;11:725–30.

3. Tan SR, Tope WD. Pulsed dye laser treatment of rosacea improves erythema, symptomatology, and quality of life. J Am Acad Dermatol 2004;51:592–9. https://doi.org/10.1016/j.jaad.2004.04.010.

4. Gether L, Overgaard LK, Egeberg A, Thyssen JP. Incidence and prevalence of rosacea: a systematic review and meta-analysis. Br J Dermatol 2018;179:282–289. https://doi.org/10.1111/bjd.16481.

5. Elewski BE, Draelos Z, Dréno B, Jansen T, Layton A, Picardo M. Rosacea - Global diversity and optimized outcome: Proposed international consensus from the Rosacea international expert group. J Eur Acad Dermatology Venereol 2011;25:188–200. https://doi.org/10.1111/j.1468-3083.2010.03751.x.

6. Demerjian M, Hachem JP, Tschachler E, Denecker G, Declercq W, Vandenabeele P, et al. Acute modulations in permeability barrier function regulate epidermal cornification: Role of caspase-14 and the protease-activated receptor type 2. Am J Pathol 2008;172:86–97. https://doi.org/10.2353/ajpath.2008.070161.

7. Stefansson K, Brattsand M, Roosterman D, Kempkes C, Bocheva G, Steinhoff M, et al. Activation of proteinase-activated receptor-2 by human kallikrein-related peptidases. J Invest Dermatol 2008;128:18–25. https://doi.org/10.1038/sj.jid.5700965.

8. Holmes AD, Steinhoff M. Integrative concepts of rosacea pathophysiology, clinical presentation and new therapeutics. Exp Dermatol 2017;26:659–67. https://doi.org/10.1111/exd.13143.

9. Whitfeld M, Gunasingam N, Leow LJ, Shirato K, Preda V. Staphylococcus epidermidis: A possible role in the pustules of rosacea. J Am Acad Dermatol 2011;64:49–52. https://doi.org/10.1016/j.jaad.2009.12.036.

10. Cap AP, Baer DG, Orman JA, Aden J, Ryan K, Blackbourne LH. Tranexamic acid for trauma patients: A critical review of the literature. J Trauma - Inj Infect Crit Care 2011;71:S9–S14. https://doi.org/10.1097/TA.0b013e31822114af.

11. Sharma YK, Gupta A. Some other serendipitous discoveries in dermatology. Indian J Dermatol 2016;61:95–96. https://doi.org/10.4103/0019-5154.174045.

12. Sadeq OR, Mowais MA. ERYTHROMYCIN: ITS GLYCEMIC EFFECT IN AN INFECTIOUS PATIENTS. Int Res J Pharm 2018;9:25–9. https://doi.org/10.7897/2230-8407.099182.

13. Two AM, Wu W, Gallo RL, Hata TR. Rosacea: Part II. Topical and systemic therapies in the treatment of rosacea. J Am Acad Dermatol 2015;72:761–70. https://doi.org/10.1016/j.jaad.2014.08.027.

14. Tan J, Berg M. Rosacea: Current state of epidemiology. J Am Acad Dermatol 2013;69:S27-s35. https://doi.org/10.1016/j.jaad.2013.04.043.

15. Halioua B, Cribier B, Frey M, Tan J. Feelings of stigmatization in patients with rosacea. J Eur Acad Dermatology Venereol 2017;31:163–8. https://doi.org/10.1111/jdv.13748.

16. Bewley A, Fowler J, Schöfer H, Kerrouche N, Rives V. Erythema of Rosacea Impairs Health-Related Quality of Life: Results of a Meta-analysis. Dermatol Ther (Heidelb) 2016;6:237–47. https://doi.org/10.1007/s13555-016-0106-9.

17. Egeberg A, Hansen PR, Gislason GH, Thyssen JP. Patients with Rosacea Have Increased Risk of Depression and Anxiety Disorders: A Danish Nationwide Cohort Study. Dermatology 2016;232:208–13. https://doi.org/10.1159/000444082.

18. Two AM, Wu W, Gallo RL, Hata TR. Rosacea: Part I. Introduction, categorization, histology, pathogenesis, and risk factors. J Am Acad Dermatol 2015;72:749–58. https://doi.org/10.1016/j.jaad.2014.08.028.

19. Del Rosso JQ, Thiboutot D, Gallo R, Webster G, Tanghetti E, Eichenfield L, et al. Consensus recommendations from the American Acne & Rosacea Society on the management of rosacea, Part 1: A status report on the disease state, general measures, and adjunctive skin care. Cutis 2013;92:234–40.

20. Draelos ZD. Assessment of skin barrier function in rosacea patients with a novel 1% metronidazole gel. J Drugs Dermatol 2005;4:557–62.

21. Steinhoff M, Buddenkotte J, Aubert J, Sulk M, Novak P, Schwab VD, et al. Clinical, cellular, and molecular aspects in the pathophysiology of rosacea. J Investig Dermatology Symp Proc 2011;15:2–11. https://doi.org/10.1038/jidsymp.2011.7.

22. Lee SE, Jeong SK, Lee SH. Protease and Protease-activated Receptor-2 signaling in the pathogenesis of atopic dermatitis. Yonsei Med J 2010;51:808–22. https://doi.org/10.3349/ymj.2010.51.6.808.

23. Schaller M, Almeida LMC, Bewley A, Cribier B, Dlova NC, Kautz G, et al. Rosacea treatment update: recommendations from the global ROSacea COnsensus (ROSCO) panel. Br J Dermatol 2017;176:465–71. https://doi.org/10.1111/bjd.15173.

24. Powell F. Clinical practice. Rosacea. N Engl J Med 2005;352:793–803. https://doi.org/10.1056/NEJMcp042829.

25. Anzengruber F, Czernielewski J, Conrad C, Feldmeyer L, Yawalkar N, Häusermann P, et al. Swiss S1 guideline for the treatment of rosacea. J Eur Acad Dermatology Venereol 2017;11:768–80. https://doi.org/10.1111/jdv.14349.

26. Yuan C, Wang XM, Yang LJ, Wu PL. Tranexamic acid accelerates skin barrier recovery and upregulates occludin in damaged skin. Int J Dermatol 2014;53:959–65. https://doi.org/10.1111/ijd.12099.

27. Na JI, Choi SY, Yang SH, Choi HR, Kang HY, Park KC. Effect of tranexamic acid on melasma: A clinical trial with histological evaluation. J Eur Acad Dermatology Venereol 2013;27:1035–9. https://doi.org/10.1111/j.1468-3083.2012.04464.x.