

Potential Role of Tranexamic Acid in Rosacea Treatment: conquering Flushing Beyond Melasma

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Abstract: Rosacea is a chronic inflammatory skin disease that affects a patient's appearance and quality of life. It mainly affects the midface region and presents as erythema, flushing, telangiectasia, papules, pustules, and rhinophyma. Despite its prevalence, the precise pathophysiology of rosacea remains unknown, and novel pharmacological therapies are currently under investigation. Tranexamic acid (TA) is a synthetic, lysine-like compound that competitively inhibits fibrinogen production by synthesizing fibrinolytic enzymes. In addition to its popular application in hemorrhage treatment, TA has been used to manage a number of skin conditions, including melasma, chronic urticaria, and angioedema. TA is a better option for melasma treatment. However, the role of TA in treating rosacea has not yet been systematically elucidated. In this study, we reviewed all available literature on the use of TA for rosacea treatment. The included articles examined the therapeutic effects of TA in patients with rosacea, including traditional methods such as oral and topical administration and more novel approaches such as intradermal injections, microneedling, and laser-assisted delivery. Several recent clinical studies demonstrated that TA alleviates rosacea symptoms by restoring the permeability barrier, ameliorating the immune reaction, and inhibiting angiogenesis. In this review, we summarized the function and potential application of TA in rosacea treatment, aiming to facilitate the implementation of clinical applications.

Keywords: rosacea, tranexamic acid, topical, oral, microinjection

Introduction

Rosacea is a chronic inflammatory dermatosis characterized by symmetric erythema, with or without flushing, mainly affecting the midface region. Clinical manifestations of rosacea include recurrent transient or persistent erythema, paroxysmal flushing, telangiectasia, papules, pustules, and rhinophyma. Patients with rosacea may also experience discomfort owing to skin irritation, dryness, and burning. Areas of erythema and flushing involve the bilateral forehead, cheeks, nose, chin, and ears. Rosacea mostly affects women aged between 30 and 50 years,¹ and its worldwide prevalence ranges from 1% to 22%.² The precise pathogenesis of rosacea remains unclear, with hypotheses that it could be associated with genetic background, abnormal innate and adaptive immunity, dysregulated neurovascular system, impaired skin barrier function, and an altered microbiome.³⁻⁶ The most common triggers are sun exposure, emotional pressure, temperature changes, and hot weather.⁷

In rosacea, several molecules related to innate immunity, including toll-like receptor 2, serine proteinase kallikrein 5 (KLK5), and cathelicidin, are overexpressed.⁸ The dermis is infiltrated by immunocytes, including mast cells, macrophages, neutrophils, and lymphocytes, and dilated vessels are observed. Considering the aforementioned pathogenesis, a series of topical and systemic medications are available for different targets. Among topical drugs, KLK5 inhibitors, including ivermectin⁹ and azelaic acid,¹⁰ selective adrenoreceptor agonists, including brimonidine and oxymetazoline, and demodex inhibitors, such as metronidazole, are most commonly used.¹¹ Among systemic medications, doxycycline inhibits the

activation of KLKs,¹² and isotretinoin and selective beta-adrenergic receptor blockers are commonly used.^{11,13} In addition, intense pulsed light has been reported to be associated with decreased expression of KLK5, inhibiting mast cell degranulation and alleviating the clinical manifestations of rosacea.¹⁴ However, post-inflammatory pigmentation may occur in patients with rosacea after the alleviation of clinical manifestations. Therefore, optimized treatment to effectively target both inflammation and post-inflammatory pigmentation is of urgent requirement.

Tranexamic acid (TA) is a derivative of the amino acid lysine and is a plasmin inhibitor known as an antifibrinolytic drug.¹⁵ TA was first introduced in the 1970s to treat melasma¹⁵ and has subsequently been used to treat post-inflammatory hyperpigmentation, Riehl's melanosis, acne-related erythema, chronic urticaria, and angioedema owing to its effects in inhibiting angiogenesis,¹⁶ inflammation,¹⁷ allergy,¹⁸ melanin synthesis,¹⁹ and aging.^{20,21} There is growing evidence that TA is effective in treating rosacea. In 2012, Kim et al first described soaking in topical TA solution as an effective approach for treating rosacea.²² Subsequently, several clinical trials have validated this effect.^{23–27} Therefore, this article aims to review the latest findings on the function of TA against rosacea and discuss its underlying mechanisms.

Materials and Methods

An extensive literature search was conducted in June 2023 using PubMed and Web of Science to compile all published articles on the use of TA for rosacea treatment. Using the search terms “rosacea” and “tranexamic acid”, 18 articles were originally selected. Only articles written in English with a focus on clinical observations were included for further study. The titles and abstracts were independently screened for relevance, and the results were scrupulously checked; this led to the final selection of six clinical studies published between 2012 and 2023 that met the criteria for inclusion in this review. For each clinical study, we determined the patient's clinical manifestations, treatment regimen, frequency of treatment, follow-up time, evaluation method of effects, results, and side effects.

Results

All articles estimated the therapeutic effects of TA in patients with rosacea following various techniques, including traditional methods, such as oral and topical applications, and new methods, such as intradermal injections, microneedling, and laser-assisted delivery. The designs and results of these studies are listed in [Table 1](#) and briefly discussed in the subsequent sections of this review.

Topical Treatment

Topical TA was used as monotherapy for rosacea in three of the six studies. In 2012, Kim et al²² first reported their preliminary observations in six patients who had irritant contact dermatitis and papulopustular rosacea or rosacea. These patients were treated five consecutive times with a topical 10% TA solution (500 mg/5 mL, total 15 mL) once or twice a week. Erythema was significantly reduced, and the mean decrease in the investigators' quartile of symptoms was 2.3. Similarly, the subjective symptoms significantly decreased in all patients on the fifth day of treatment, and the mean decreases in visual analog scales (0–10) for itching, flushing, and burning were 3.8, 1.5, and 3.5, respectively. In 2015, in a retrospective study by Zhong et al,²³ 30 patients with rosacea were treated with topical 5% TA solution twice a day for 2 weeks. After the 2-week treatment period, fewer inflammatory lesions were observed. The investigators' assessments revealed a reduction in the number of lesions, such as papules and pustules, by 5.5 on the treated side and four on the control side. Skin biophysical functions, such as trans-epidermal water loss, skin surface pH, and stratum corneum hydration, improved remarkably following treatment. In 2019, Jakhar et al²⁷ conducted a study using the same concentration of TA in patients diagnosed with erythematotelangiectatic steroid-induced rosacea and melasma. The severity of erythema, telangiectasia, and burning sensation improved after topical 10% TA solution was administered twice daily for 4–6 weeks, together with clinical improvement of melasma.

In 2018, Bageorgou et al²⁵ compared the effects of 10% TA solution alone with those of a combination of 10% TA solution and microneedling to treat rosacea. In their study, 10 patients were treated for erythematotelangiectatic rosacea (ETR) with a wet dressing infused with 10% TA solution for 20 min every 15 days for four sessions; an additional ten patients were treated with a combination of microneedling and wet dressing therapy. The results showed significant improvements in the clinical severity and quality of life in both groups. The results of the combination therapy group

Table I Study Design and Results

Year	Authors	Location	Number of Patients	Sex	Age (Years)	Type of Rosacea	Treatment Method of TA	Frequency of TA	Other Treatments	Result	Follow-Up Time	Side Effects	Remarks
2012	Kim et al ²²	Korea	6	Female	48.8±10.8	Papulopustular rosacea or rosacea with irritant contact dermatitis	Wet gauze dampened with 10% TA solution	Once or twice a week, five times for 2–4 weeks	None	IQS decreases 2.3, VAS decreases 3.8 (itching), 1.5 (flushing), 3.5 (burning)	Not mentioned	Not mentioned	Two patient's refractories to oral minocycline and metronidazole gel or topical calcineurin inhibitor were responsive to TA solution soaking.
2015	Zhong et al ²³	China	30	18 females and 12 males	39.34 ±11.43	Rosacea, mostly with papules and pustules	Topical 5% TA solution	Twice daily for 2 weeks	None	The investigators' assessment decrease on the treated side	Not mentioned	Not mentioned	None
2016	Kwon et al ²⁴	Korea	1	Female	37	Erythematotelangiectatic rosacea	Oral TA	250 mg daily for 1 month	Oral combination of propranolol and minocycline	Erythema and subjective symptoms decreased.	2 months	None	None
2018	Bageorgou et al ²⁵	Greece	20	Female	27–65	Erythematotelangiectatic rosacea	Wet dressing with 10% TA, and microneedling with TA followed by 10% TA infused dressing	Every 15 days for four sessions	None	IGA-RSS decreases, DLQI increases, photographs and dermoscopic pictures decrease	4 months	None of the patients in group treated only by TA dressing suffered any adverse effects. those treated by TA microneedling and dressing caused mainly as a result of microneedling subsided a few hours after the procedure	None

(Continued)

Table I (Continued).

Year	Authors	Location	Number of Patients	Sex	Age (Years)	Type of Rosacea	Treatment Method of TA	Frequency of TA	Other Treatments	Result	Follow-Up Time	Side Effects	Remarks
2019	Jakhar et al ²⁷	India	1	Female	Not mentioned	Erythematotelangiectatic steroid-induced rosacea with melasma	Topical 10% TA solution with a cotton bud	Twice daily for 4–6 weeks	None	Erythema, telangiectasia and burning sensation reduced considerably,	Not mentioned	Not mentioned	None
2021	Daadaa et al ²⁶	Tunisia	6	3 females and 3 males	49.5±14.6	Erythematotelangiectatic rosacea	Inject intradermally with 5% TA solution	Monthly for 5.1±1.3 times	None	The mean decrease of IGA-RSS was 2.4±0.5	3 months	Transient erythema and swelling, were noticed in three cases	Melasma was also improved.

Abbreviations: TA, tranexamic acid; IQS, investigator 's quartile score; VAS, visual analog scales; IGA-RSS, investigator global assessment of rosacea severity score; DLQI, dermatology life quality index.

were marginally better than those of the TA-only group. However, in the TA-only group, the patients did not experience any adverse reactions, whereas in the combination group, the main adverse effects were caused by microneedling, which manifested as erythema, flushing, irritation, and a tingling/burning sensation, which subsided within a few hours after the procedure.

Systemic Treatment

One study serendipitously discovered that combination therapy with oral TA, propranolol, and minocycline could alleviate the clinical symptoms of rosacea. In 2016, it was found that a combination treatment of 250 mg oral TA, 40 mg propranolol, and 50 mg minocycline daily improved erythema and subjective symptoms in one patient with rosacea.²⁴ No adverse reactions were observed during the 2-month follow-up period.

Energy- or Microneedling-Assisted Delivery

One study investigated the effects of energy- or microneedling-assisted TA delivery in patients with rosacea. In 2021, intradermal microinjection of 5% TA solution was first used monthly to treat six patients with ETR.²⁶ After 3.8–6.4 months of treatment, the investigator's global assessment of rosacea severity score (IGA-RSS) was significantly reduced. Clinical improvements were maintained for at least 3 months after treatment in five patients, and only transient erythema and swelling were reported in three patients after treatment.

Discussion

Rosacea is a common inflammatory skin condition characterized by recurrent, transient, or persistent erythema and paroxysmal flushing that occurs mainly in the midface region. Studies have shown that physical symptoms and emotional distress reduce the quality of life in patients with rosacea.²⁸ Currently, the principal treatment options for rosacea include oral tetracycline, isotretinoin, β -adrenergic receptor blockers, topical antibacterial drugs, and vasoconstrictors.¹

In the previously mentioned six clinical studies, TA was reported to be effective in the treatment of rosacea. Sixty-four study subjects were assessed, including 28 patients with ETR in four studies and 36 with papulopustular rosacea in two studies without ocular rosacea or rhinophyma. Furthermore, the study duration ranged from 0.5–6.4 months, and the follow-up time was 2–3 months. No patients were lost to follow-up. In addition, three studies monitored the effects of topical TA solution for 2–6 weeks; however, no follow-up time was mentioned. One study compared the efficacy of topical TA solution alone with that of topical TA solution in combination with microneedling and monitored the results for 2 months. Notably, there was no recurrence of rosacea after stopping therapy for at least 4 months. One study evaluated a combination of oral TA, propranolol, and minocycline for 2 months. One study examined a physical method of delivering TA and continued treatment for 3.8–6.4 months, with an additional follow-up time of 3 months. In the two case reports, the investigators used subjective evaluation indicators. Erythema, telangiectasia, and subjective symptoms, including a burning sensation, were observed. In contrast, all four cohort studies used objective evaluation indicators, and two used both objective and subjective evaluation indicators. Three studies used the IGA-RSS, which was more reliable and valid within and between raters, and one study measured the lesion counts of papules and pustules. In addition to objective clinical presentations, researchers also compared the subjective symptoms of patients with rosacea. Of the four cohort studies, two adopted the widely used visual analog scales and dermatology life quality index.

No severe adverse effects were reported in any of the studies, and oral TA treatment showed no side effects.²⁴ In patients treated with the combination of TA microneedling and dressing, erythema, flushing, irritation, exfoliation, and stinging and burning sensations were observed but disappeared within hours.²⁵ Transient erythema and swelling were also reported in three patients treated with intradermal injections of TA.²⁶ Three studies reported no adverse effects.^{22,23,27}

The underlying mechanisms of TA in rosacea treatment are unknown. Two experimental studies focused on the effect of TA on the function of the skin permeability barrier,²³ immune reactions, and angiogenesis.¹⁷ TA is a plasmin inhibitor used to prevent abnormal fibrinolysis and exerts its effect by reversibly blocking lysine-binding sites on plasminogen molecules, hindering the physical interaction between the urokinase-type plasminogen activator and the stratum corneum,^{29,30} thereby inhibiting the conversion of plasminogen to plasmin. Plasmin contributes to the impairment of skin barrier function by activating the epidermal growth factor receptor signaling pathway.^{5,31,32} In addition, it is thought

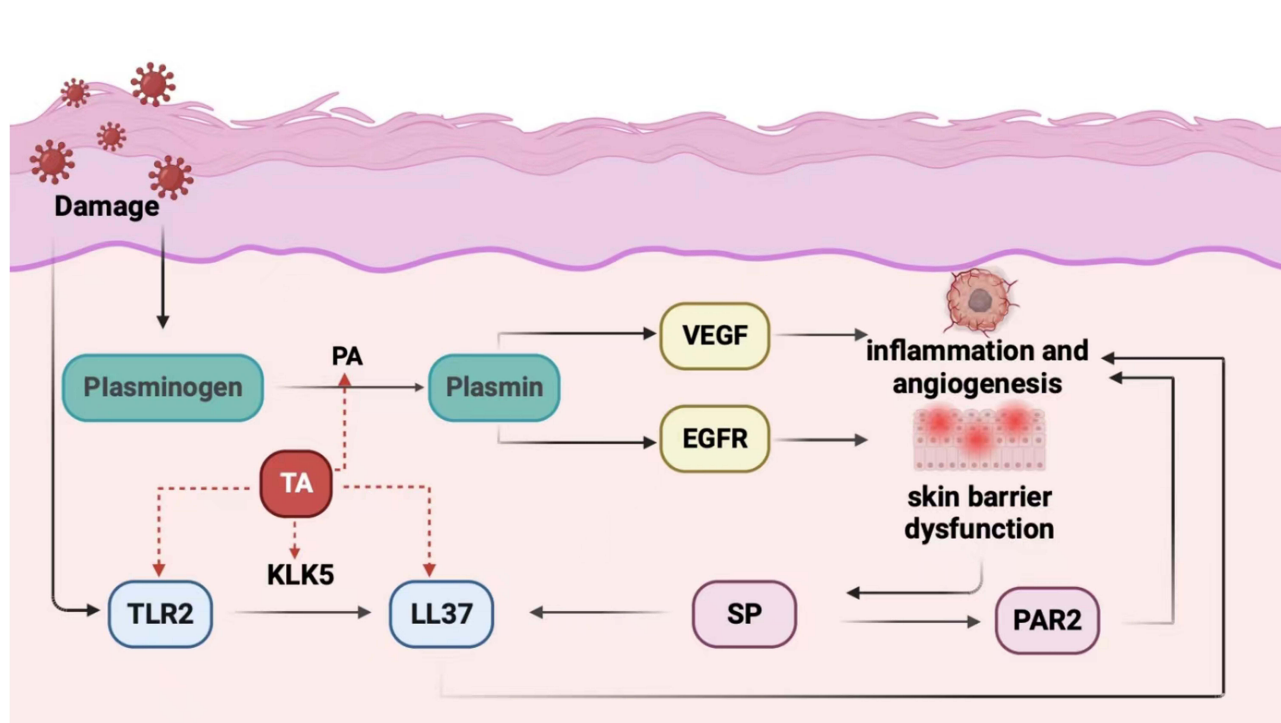


Figure 1 Possible mechanisms of tranexamic acid in rosacea treatment.

Abbreviations: PA, plasminogen activator; TA, tranexamic acid; KLK5, serine proteinase kallikrein 5; TLR2, toll-like receptor 2; VEGF, vascular endothelial growth factor; EGFR, epidermal growth factor receptor; SP, serine protease; PAR2, protease-activated receptor 2.

to convert vascular endothelial growth factor into freely diffusible forms that promote angiogenesis and inflammation.³³ One study found that treatment of LL37-induced rosacea-like dermatitis with TA resulted in decreased expression of some immune-related genes (including KLK5, CAMP, toll-like receptor 2, IL-6, and TNF- α) and immune cell (including neutrophils, mast cells, macrophages, and CD4⁺ T cells) aggregation, a decrease in the number of CD31 microvessels, and a decrease in vascular endothelial growth factor expression.¹⁷ Hence, TA may alleviate the clinical manifestations of rosacea via at least two pathways: regulating the immune response and reducing angiogenesis. Another study suggested that while the skin barrier is impaired, serine protease activation further elevates the production of protease-activated receptor 2 and active forms of LL37, which could result in inflammation and angiogenesis.²³ The mechanisms underlying the successful treatment of rosacea by TA might be attributed to improved function of the permeability barrier owing to the prevention of serine protease activity in human skin samples and HaCaT cells. The mechanisms that have been clarified thus far are depicted in Figure 1. Furthermore, one study reported the combination usage of oral propranolol, minocycline and TA had alleviated the clinical severity of rosacea. However, it is not yet clear which one plays a major role, and whether a synergistic mechanism exists among these drugs. Nevertheless, further studies are required to clarify the detailed functional mechanisms of TA in the treatment of rosacea.

Although the aforementioned studies have revealed that TA could serve as an effective and safe modality for rosacea treatment, there are several gaps in the current literature. Well-designed, randomized, double-blind, placebo-controlled clinical trials with larger sample sizes are required to further validate these effects, excluding other confounding factors, such as emotional changes, environmental changes, and additional oral or topical medications. Moreover, different types of rosacea have different pathogeneses; therefore, future studies should explore whether TA is effective for other subtypes of rosacea.

Conclusions

According to the literature, oral TA may be a better option for melasma treatment.³⁴ In addition, TA has demonstrated a growing significance in the management of post acne erythema^{35,36} and rosacea erythema. Accordingly, TA may be

a more favorable treatment option for rosacea with concomitant melasma. Both clinical and experimental studies have demonstrated the potential of TA for the treatment of rosacea by regulating skin barrier function and immune reactions, as well as reducing angiogenesis. More large-sample, double-blind, randomized controlled studies with longer follow-up periods are needed to determine the efficacy, optimal dosage and route of administration, relapse rates, and potential side effects of TA. This review thoroughly summarizes the currently known function and potential application of TA in rosacea treatment, facilitating the implementation of clinical applications.

Abbreviations

EGFR, epidermal growth factor receptor; ETR, erythematotelangiectatic rosacea; IGA-RSS, investigator global assessment of rosacea severity score; KLK5, serine proteinase kallikrein 5; PA, plasminogen activator; PAR2, protease-activated receptor 2; SP, serine protease; TA, tranexamic acid; TLR2, toll-like receptor 2; VEGF, vascular endothelial growth factor.

Data Sharing Statement

The data was obtained from PubMed and Web of Science.

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Disclosure

The authors report no conflicts of interest.

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