Treatment of Melasma Using Tranexamic Acid: What's Known and What's Next

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RESIDENT **PEARL**

- Oral tranexamic acid is an antifibrinolytic agent that can be used off-label for the treatment of melasma.

Tranexamic acid is a procoagulant agent that is approved by the US Food and Drug Administration for treatment of menorrhagia and to prevent hemorrhage in patients with hemophilia undergoing tooth extractions. Through its inhibitory effects on the plasminogen activation pathway, tranexamic acid also mitigates the UV radiation–induced pigmentation response. Systemic tranexamic acid has consistently been reported as an effective treatment of melasma, though its broad use may be limited by the risk for thromboembolism. Limited studies have investigated the efficacy of topical tranexamic acid, with or without the use of adjunctive therapies to increase uptake. This review summarizes the effects of tranexamic acid on the pathophysiology of melasma and the available evidence on the off-label treatment of melasma using systemic and topical tranexamic acid.

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Tranexamic acid is a synthetic lysine derivative that inhibits plasminogen activation by blocking lysine-binding sites on the plasminogen molecule. Although the US Food and Drug Administration–approved indications for tranexamic acid include treatment of patients with menorrhagia and reduction or prevention of hemorrhage in patients with hemophilia undergoing tooth extraction, the potential efficacy of tranexamic acid in the treatment of melasma has been consistently reported since the 1980s.[1]

Tranexamic acid exerts effects on pigmentation via its inhibitory effects on UV light–induced plasminogen activator and plasmin activity.[2] UV radiation induces the synthesis of plasminogen activator by keratinocytes, which results in increased conversion of plasminogen to plasmin. Plasminogen activator induces tyrosinase activity, resulting in increased melanin synthesis. The presence of plasmin results in increased production of both arachidonic acid and fibroblast growth factor, which stimulate melanogenesis and neovascularization, respectively.[3] By inhibiting plasminogen activation, tranexamic acid mitigates UV radiation–induced melanogenesis and neovascularization. In treated guinea pig skin, application of topical tranexamic acid following UV radiation exposure inhibited the development of expected skin hyperpigmentation and also reduced tyrosinase activity.[4,5]

The largest study on the use of oral tranexamic acid for treatment of melasma was a retrospective chart review of 561 melasma patients treated with tranexamic acid at a single center in Singapore.[6] More than 90% of patients received prior treatment of their melasma, including bleaching creams and energy-based treatment. Among patients who received oral tranexamic acid over a 4-month period, 90% of patients demonstrated improvement in their melasma severity. Side effects were experienced by 7% of patients; the most common side effects were abdominal bloating and pain (experienced by 2% of patients). Notably, 1 patient developed deep vein thrombosis during treatment and subsequently was found to have protein S deficiency.[6]

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Although the daily doses of tranexamic acid for the treatment of menorrhagia and perioperative hemophilia patients are 3900 mg and 30 to 40 mg/kg, respectively, effective daily doses reported for the treatment of melasma have ranged from the initial report of efficacy at 750 to 1500 mg to subsequent reports of improvement at daily doses of 500 mg.[1,2,6-8]

Challenges to the use of tranexamic acid for melasma treatment in the United States include the medicolegal environment, specifically the risks associated with using a systemic procoagulant medication for a cosmetic indication. Patients should be screened and counseled on the risks of developing deep vein thrombosis and pulmonary embolism prior to initiating treatment. Cost and accessibility also may limit the use of tranexamic acid in the United States. Tranexamic acid is available for off-label use in the United States with a prescription in the form of 650-mg tablets that can be split by patients to approximate twice-daily 325 mg dosing. This cosmetic indication poses an out-of-pocket cost to patients of over $110 per month or as low as $48 per month with a coupon at the time of publication.[9]

Given the potential for serious adverse effects with the use of systemic tranexamic acid, there has been interest in formulating and evaluating topical tranexamic acid for cosmetic indications.[10-13] Topical tranexamic acid has been used alone and in conjunction with modalities to increase uptake, including intradermal injection, microneedling, and fractionated CO_2 laser.[12-14] Although these reports show initial promise, the currently available data are limited by small sample sizes, short treatment durations, lack of dose comparisons, and lack of short-term or long-term follow-up data. In addition to addressing these knowledge gaps in our understanding of topical tranexamic acid as a treatment option for melasma, further studies on the minimum systemic dose may address the downside of cost and potential for complications that may limit use of this medication in the United States.

The potential uses for tranexamic acid extend to the treatment of postinflammatory hyperpigmentation and rosacea. Melanocytes cultured in media conditioned by fractionated CO_2 laser–treated keratinocytes were found to have decreased tyrosinase activity and reduced melanin content when treated with tranexamic acid, suggesting the potential role for tranexamic acid to be used postprocedurally to reduce the risk for postinflammatory hyperpigmentation in prone skin types.[15] Oral and topical tranexamic acid also have been reported to improve the appearance of erythematotelangiectatic rosacea, potentially relating to the inhibitory effects of tranexamic acid on neovascularization.[3,16,17] Although larger-scale controlled studies are required for further investigation of tranexamic acid for these indications, it has shown early promise as an adjunctive treatment for several dermatologic disorders, including melasma, and warrants further characterization as a potential therapeutic option.

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