

# Wet Your Whistles: Alcohol-Induced Flushing With Use of Topical Calcineurin Inhibitors

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Localized flushing after alcohol ingestion is a reported adverse effect of 2 topical calcineurin inhibitors, tacrolimus and pimecrolimus, which are approved to treat atopic dermatitis and used off label for other dermatologic conditions. We propose techniques for alleviating this phenomenon.

*Cutis.* 2022;109:170-171.

## Practice Gap

The topical calcineurin inhibitors (TCIs) tacrolimus and pimecrolimus are US Food and Drug Administration approved for the treatment of atopic dermatitis.<sup>1</sup> In addition, these 2 drugs are utilized off label for many other dermatologic conditions, including vitiligo, psoriasis, and periorificial dermatitis. They can be used safely for prolonged periods and on sensitive areas, including the face.

Treatment with a TCI provides advantages over topical steroids, which can cause atrophy, telangiectasia, dyspigmentation, ocular hypertension, cataracts, and tachyphylaxis after prolonged use. Adverse events resulting from use of a TCI most commonly include transient burning, warmth, and erythema in areas of application. Patients typically acclimate to these effects after a few consecutive days of use.

Localized flushing after alcohol ingestion is a known potential side effect of TCIs<sup>1</sup>; however, this association may be underappreciated and underreported to patients.

## Counseling Patients Taking TCIs

Topical calcineurin inhibitors cause alcohol-induced flushing on areas of application (Figures 1 and 2) in approximately 3.4% to 6.9% of patients.<sup>1</sup> The reaction

has been reported with both topical TCIs but more often is noted with tacrolimus.<sup>2,3</sup> Typically, flushing begins 2 to 4 weeks after treatment is initiated and within 5 to 20 minutes after alcohol intake.<sup>4</sup> The phenomenon is self-limited; erythema typically resolves in 20 to 60 minutes.

Topical calcineurin inhibitors are hypothesized to cause alcohol-induced flushing by locally inhibiting acetaldehyde dehydrogenase, an enzyme necessary for alcohol metabolism. This leads to accumulation of acetaldehyde, a by-product of alcohol metabolism, which indirectly causes concentrated vasodilation by means of prostaglandins, histamines, and other vasodilatory mediators. The combination of ethanol and a TCI also might induce release of neuropeptides, which could cause vasodilation.<sup>4</sup>

Alcohol-related flushing commonly is seen among individuals who are aldehyde dehydrogenase 2 (ALDH2) deficient; it is sometimes accompanied by nausea, headache, and tachycardia. The same pathway is implicated in disulfiram reactions, to a more intense and systemic degree, to discourage alcohol intake.

Oral calcineurin inhibitors are not reported to cause generalized flushing, perhaps because of differences in the relative dose. For example, topical tacrolimus 0.1% is 1 mg/g that is applied to a relatively small body surface area; oral calcineurin inhibitors are dosed at a range of 1 to 15 mg for an entire person.

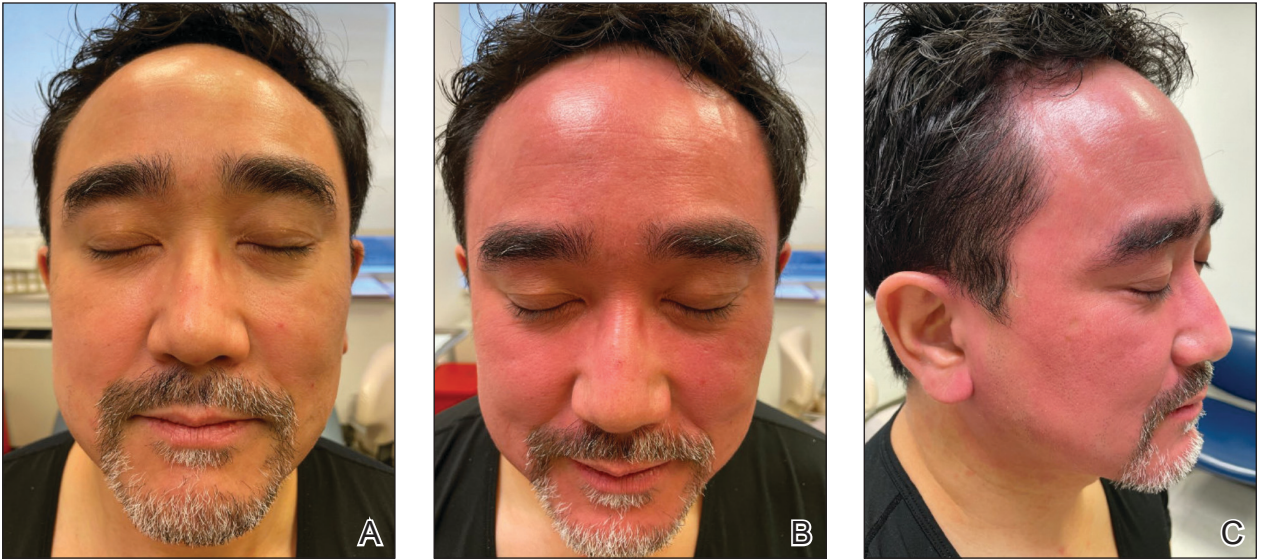
Notably, erythema that develops after alcohol intake in a patient taking a topical TCI can mimic the dermatosis being treated—similar to one of our patients (Figure 2) whose flushing was mistaken for a flare of periorificial dermatitis—contact dermatitis or another flushing disorder

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Dr. Milam reports no conflict of interest. Dr. Cohen is/was a consultant for or has received honoraria from Asana BioSciences; Cosmetic Ingredient Review; Dermavant Sciences, Inc; Ferndale Pharma Group, Inc; FIDE (which receives industry sponsorship from AbbVie, Arena Pharmaceuticals, Arcutis Biotherapeutics, Inctye, Janssen Pharmaceuticals, LEO Pharma, Pfizer, Sanofi Regeneron, Sun Pharma, and UCB); LEO Pharma; Novartis; SFJ Pharmaceuticals, Inc; and UCB. He also holds or has held stock in or has received stock options from Brickell Biotech; Dermira; Evommune, Inc; Kadmon Corporation; Medimetriks Pharmaceuticals; and Timber Pharmaceuticals. He is or has been on the Board of Directors for Dermira; Evommune, Inc; Kadmon Corporation; Sanofi; and Timber Pharmaceuticals.

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doi:10.12788/cutis.0478



**FIGURE 1.** A man with atopic dermatitis that requires application of a topical calcineurin inhibitor (tacrolimus ointment 0.1%) to the entire face. A, Patient prior to ingesting alcohol. B and C, Twelve minutes after consuming 1 beer (12 oz), the patient exhibited profound flushing of the entire face, with sharp demarcation at the neck where the topical calcineurin inhibitor was not applied. He denied a history of alcohol intolerance.



**FIGURE 2.** A woman for whom the topical calcineurin inhibitor pimecrolimus cream 1% had been prescribed for periorificial dermatitis. She noted erythema and a “burning” sensation restricted to areas where pimecrolimus had been applied within 20 minutes after an alcoholic drink.

such as rosacea. Uninformed patients might mistakenly self-diagnose the flushing as an allergic or anaphylactic reaction to foods, drugs, or other exposures contemporaneous with alcohol ingestion. The side effect can be frustrating owing to its appearance and discomfort, which often coincide with social interactions involving alcohol.

### Techniques to Avoid Flushing

Discontinuing a TCI altogether leads to resolution of associated adverse effects, including flushing, typically within weeks to 1 month.<sup>5</sup> Alternatively, oral aspirin (81 mg) might eliminate or attenuate symptoms, as documented in a double-blind, controlled trial in

which relief of TCI-induced flushing after consuming wine was investigated.<sup>6</sup>

Another approach (albeit nontraditional) is for patients who experience this phenomenon to “wet their whistles” with an alcoholic drink before a social engagement. After flushing resolves in 20 to 60 minutes, subsequent drinks do not appear to elicit symptoms again in most patients. That said, we stop short of calling this tip “doctor’s orders.”

### Practical Implication

Counseling patients who will be using a TCI—tacrolimus or pimecrolimus—about the potential for these drugs to produce localized flushing after alcohol ingestion as well as techniques for lessening or eliminating this adverse effect are important facets of their dermatologic care.

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