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Topical Oxymetazoline (Rhofade) in Rosacea

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ABSTRACT: By definition, a drug is a medicine or substance that exerts a physiologic effect on an organism. In dermatology, various medications and substances are utilized on a daily basis, ranging from topical treatments to anesthetics in micrographic surgery. The purpose of this section is to focus on some of the more common substances, specifically how they work, how they are utilized, and routine alternatives (if available). The mechanism of action, usage, and alternative options of the medication topical oxymetazoline are discussed.

Key words: *Demodex folliculorum*, Erythematotelangiectatic, Oxymetazoline, Rhofade, Rosacea

Rosacea is a common and chronic relapsing inflammatory dermatosis primarily affecting the cheeks, nose, chin, and forehead. The cutaneous manifestations are diverse but are characterized by persistent facial erythema, telangiectasias, inflammatory papules and pustules, facial flushing, nonpitting facial edema, and sometimes phymatous growth (Two et al., 2015) Depending on the predominant feature, rosacea may be classified into one of four different subtypes including erythematotelangiectatic, papulopustular, phymatous, and ocular (Two et al., 2015). The erythema of rosacea can be further subdivided into (a) sole erythema, (b) erythema with telangiectasias, (c) erythema with edema, and (d) erythema with inflammatory papules and nodules (Wollina, 2014). Diffuse facial erythema must be distinguished from the perilesional erythema associated with inflammatory lesions to optimize treatment (Del Rosso, 2012; Wollina, 2014).

The most common form is the erythematotelangiectatic type, which presents with persistent centrofacial erythema and telangiectasia, without additional inflammatory lesions (Del Rosso et al., 2013; Hoover & Erramouspe, 2018). The redness is maintained in between flares, although it may be exacerbated by certain triggers such as alcohol, spicy foods, and increased sun exposure (Hoover & Erramouspe, 2018). Although the pathogenesis has yet to be fully elucidated, rosacea is thought to be related to overgrowth of skin organisms, dysregulation of the innate immune system, and aberrant signaling of the neurovascular system (Two et al., 2015). Significantly higher levels of *Demodex folliculorum*, a saprophytic mite that resides in the pilosebaceous unit, have been reported in several studies done on patients with rosacea. The facial erythema of rosacea correlates with the increased density and diameter of the underlying vasculature, which is modulated by the sympathetic nervous system (Del Rosso, 2017). In addition, cathelicidin peptide (LL-37), an antimicrobial peptide, is elevated in rosacea skin. Although topical antibiotics have a role in controlling the underlying bacterial infection associated with the inflammation seen in rosacea, they are not as effective in controlling the inflammatory factors that lead to vasodilation and redness in erythematotelangiectatic rosacea (Del Rosso, 2013). These superficial blood vessels are encased by a sheath of smooth muscles, which allow for vasoconstriction after alpha-1-adrenergic receptor agonism. Constriction of these blood vessels may significantly reduce facial erythema, although it will not affect capillaries nor telangiectasias as the adrenergic effect is limited to the

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precapillary arterioles (Del Rosso, 2013, 2017; Fowler et al., 2015; Shanler & Ondo, 2007).

Emergence of Oxymetazoline in Facial Erythema

Treatment of rosacea often incorporates multiple modalities, ranging from topical drugs to oral drugs and combination therapy (Staedtler et al., 2017). To modulate vasculature activity, topical alpha-adrenergic receptor agonists were developed and have been found to be effective in decreasing facial erythema. The alpha-1-adrenergic agonist, oxymetazoline, has been historically used for nasal congestion, as it constricts the vessels of the nasal mucosa when applied intranasally. The vasoconstrictive properties of this medication are now being applied for the management of cutaneous diseases such as rosacea. In January 2017, the Food and Drug Administration approved oxymetazoline hydrochloride 1% cream (Rhofade, Allergan Pharmaceuticals, Irvine, CA) for the treatment of rosacea. Data were taken from two randomized controlled trials where the safety and efficacy of topical oxymetazoline hydrochloride 1% cream were evaluated for the treatment of persistent facial erythema of rosacea. Eight hundred eighty-five patients with moderate-to-severe facial erythema related to rosacea were enrolled, with 79% of patients being female and 90% being White. Patients were randomized into two groups, with 489 receiving oxymetazoline and 483 given vehicle. They were instructed to apply the creams topically to the face once daily for 29 days. On the 29th day, facial erythema was analyzed at 3, 6, 9, and 12 hours postdose. Facial erythema was evaluated on both patient- and clinician-reported 5-point scales, and the combination of this value was used to determine the number of patients experiencing a 2-point improvement from baseline. Results showed a significant decrease in facial erythema using oxymetazoline (12%–18%) at each time point compared with vehicle (5%–9%). In the long-term open-label study lasting 52 weeks, oxymetazoline continued to show similar results in which oxymetazoline was found to be superior to vehicle, therefore establishing efficacy of the drug. Furthermore, the clinical trials were designed to evaluate for rebound erythema after discontinuation of the topical medication. There was no indication either on the package inserts or in the clinical trial data to indicate posttreatment rebound, intermittent flushing, or worsening of facial erythema after discontinuation of the oxymetazoline (Del Rosso, 2017; Hoover & Erramouspe, 2018).

Adverse Effects

In the clinical trials, topical treatment with oxymetazoline was well tolerated with adverse effects being mild to moderate in severity. Side effects in patients applying oxymetazoline every day for 29 days included application site dermatitis (2%), worsening inflammatory lesions of rosacea (1%), pruritus at application site (1%), erythema (1%), and pain (1%; Katzung et al., 2017). The long-term clinical trial had similar adverse effects, with similar rates: worsening inflammatory lesions of rosacea (3%), application site dermatitis (3%), pruritus (2%), pain (2%), and erythema (2%; LexiComp, 2020; Litt & Shear, 2017). In both studies, the worsening of facial erythema was minimal during active treatment and after discontinuation of therapy with topical oxymetazoline, suggesting this is an uncommon side effect (Del Rosso, 2017).

Alternatives

The first topical medication approved for persistent facial erythema of rosacea was brimonidine 0.33% (brimonidine tartrate 0.5%) gel in August 2014. Brimonidine differs from oxymetazoline by its selective action on alpha-2 adrenergic receptors where it also acts as a vasoconstrictor of the superficial vasculature ("Mirvaso," 2016). Brimonidine onset of action is approximately 30 minutes and lasts up to 6 hours. Adverse effects of topical brimonidine include flushing (10%), erythema (8%), rosacea (5%), nasopharyngitis (5%), skin burning sensation (4%), increased intraocular pressure (4%), and headache (4%). Moreover, data from the brimonidine clinical trials describe that some subjects experienced rebound erythema that was worse in severity when compared with baseline, an adverse effect that was not seen with topical oxymetazoline ("Mirvaso," 2016).

Currently, there are no studies comparing the safety and efficacy of oxymetazoline with that of brimonidine. Using the results from the existing clinical trials to make a comparison is difficult because of the different measurement scales used in each study. The Clinical Erythema Assessment scale and Patient Self-Assessment scale were utilized in the brimonidine studies, whereas the Clinical Erythema Assessment and Subject Self-Assessment scales were utilized in the oxymetazoline studies (Hoover & Erramouspe, 2018; Fowler et al., 2015). Although both assessments are based on 5-point scales, there are different definitions for each point, and therefore no correlation can be drawn between the two studies (Hoover & Erramouspe, 2018). Further research to determine the therapeutic differences between these two medications is still needed.

CONCLUSIONS

Rosacea is a common facial dermatosis, and the appearance associated with this disease has been found to negatively impact the quality of life by creating stigmatizing feelings and anxiety in these patients (Duman et al., 2014). Although many therapies are available for the treatment of rosacea, the optimal therapy for the management of facial erythema has yet to be established. On the basis of current research, topical alpha-adrenergic agonist therapies have proven to be safe and effective and are currently the only agents offered to specifically target the facial erythema of rosacea. Topical 1% oxymetazoline should now be considered in the armamentarium of medications used for facial erythema

in rosacea, as data suggest that it is an efficacious alternative with minimal side effects compared with previously approved topical medications.

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