

# Successful Treatment of the Erythema and Flushing of Rosacea Using a Topically Applied Selective $\alpha_1$ -Adrenergic Receptor Agonist, Oxymetazoline

Stuart D. Shanler, MD; Andrew L. Ondo, MD; School of Medicine, University of New Mexico, Albuquerque (Dr Ondo). Dr Shanler is in private practice in New York, New York.

*The Cutting Edge: Challenges in Medical and Surgical Therapeutics*

The erythematotelangiectatic (ETR) subtype of rosacea is characterized by frequent episodes of facial flushing and persistent centrofacial erythema and may be accompanied by telangiectasias, facial edema, burning, or stinging. The pathophysiologic cause of the erythema is uncertain, and there are currently no satisfactory treatments for this common form of rosacea.

## REPORT OF CASES

### CASE 1

A 55-year-old man presented with a long history of ETR rosacea manifesting with prolonged facial flushing provoked by multiple stimuli including heat, exercise, sun exposure, and the consumption of alcoholic beverages. He confided that he was particularly disturbed that, for many years, people frequently asked him: "Why is your face so red?" His condition had progressed over the last 15 years to include persistent facial erythema. In addition to his usual triggers, he had noted that during his workday in an air conditioned office the erythema worsened, usually peaking in early afternoon, sometimes with concurrent facial stinging or burning. He had previously been treated with several oral antibiotics, multiple topical therapies including metronidazole, and most recently azelaic acid gel, with no effect. He asked if there was anything that might help the erythema and symptoms.

### CASE 2

A 70-year-old woman presented with a history of ETR rosacea, progressively worsening throughout her adult life. Although she had endured episodic flushing for decades, her erythema had become persistent in recent years. She had used numerous topical antibiotics for decades, including metronidazole, clindamycin phosphate, and combination sodium sulfacetamide, 10%, and precipitated sulfur, 5%, in an attempt to alleviate the erythema. She noted no improvement with the use of any of these agents and stated that she had continued using them "more out of hope" than because the medications had any effect. She had also used topical tretinoin with no

improvement and had considered pulsed-dye laser therapy but had decided against it.

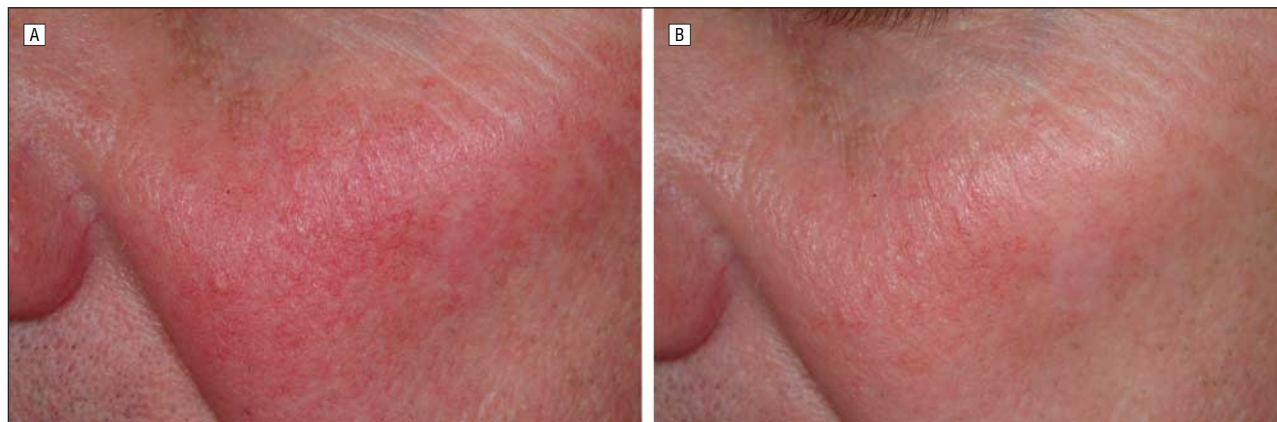
## THERAPEUTIC CHALLENGE

Erythematotelangiectatic rosacea, in general, responds poorly to treatment. Topical and oral antibiotics, standard treatment for papulopustular rosacea, are usually ineffective. Oral systemic agents such as  $\beta$ -blockers, clonidine hydrochloride, and spironolactone have little evidence of benefit; these agents also have potential systemic adverse effects. The pulsed-dye laser and, more recently, other nonablative laser and light therapies have been used to treat erythema and telangiectasias; however, not all patients respond, multiple treatment sessions are required, recurrences are common, costs can be significant, and flushing is often persistent. Our 2 patients demonstrate typical features of ETR rosacea with easily triggered, treatment resistant, socially embarrassing, persistent facial erythema and discomfort (stinging and burning). Neither patient demonstrated a papulopustular component, phymatous component, or ocular component to their disease, and conventional therapeutic options had not been effective.

## SOLUTION

An attempt to treat ETR rosacea using an over-the-counter drug known to possess vasoconstrictive properties was undertaken. A commercially available preparation of oxymetazoline hydrochloride, 0.05%, solution was applied once daily to the affected area of the face.

Patient 1 and her physician (1 of us) (A.L.O.) noted a decrease in facial erythema within 1 hour of drug application, and a dramatic improvement within 2 to 3 hours. This effect was sustained throughout the entire day. After a 7:30 AM application of the drug, the patient noted an improvement in the chronic "baseline" erythema, and experienced a marked reduction in his transient flares. His erythema continued to be controlled in the early afternoon, at his normal time of peak erythema, and he experienced no stinging or burning (**Figure**).



**Figure.** Baseline photograph of patient 1 immediately prior to application of oxymetazoline, 0.05%, solution (A) and 3 hours after topical application (B), demonstrating marked improvement in macular erythema and fine telangiectasias.

Patient 2 reported a similar improvement in her appearance and symptoms. Two weeks after initiating therapy, she was so pleased with the response that she sent her physician (1 of us) (A.L.O.) a letter of thanks indicating that the treatment was still effective and that she had discontinued use of topical metronidazole, her most current treatment. She returned 3 months after initiating therapy and continued to evidence marked improvement in the erythema and had experienced no episodic flares or flushing.

Both patients were counseled that this treatment was “off label” and that even though the medication was over the counter, adverse effects could occur and could include the listed adverse effects of underlying heart disease, hypertension, thyroid disease, diabetes mellitus, and urinary retention. Both patients elected to continue treatment on their own. Patient 1 stated that “This is the first time my face has been normal in decades.” Six weeks after initiating once-daily application, patient 1 demonstrated continued control of the erythema and had complete relief of his facial stinging and burning. Neither patient experienced any adverse effects, has evidenced any rebound flares in erythema or other symptoms, or has demonstrated any tachyphylaxis to the current regimen. At the last follow-up examination, patient 1 had continued treatment for 8 months and patient 2 for 17 months, with sustained effects. Both patients had discontinued all other therapies directed toward their rosacea other than sunscreen use.

#### COMMENT

Rosacea is a common, chronic cutaneous disorder, the clinical manifestations and subtypes of which have been very well described and recently reviewed.<sup>1-3</sup> Erythematotelangiectatic rosacea is the subtype of rosacea most characterized by its frequent episodes of transient facial erythema (flushing) and nontransient, or persistent, erythema. It may be accompanied by facial edema, burning, or stinging.<sup>3</sup> While rosacea remains a disorder of uncertain etiology and pathogenesis, the abnormal flushing and persistent erythema have usually been theorized to arise from a dysregulation in the cutaneous vasomotor response, which, whether triggered by neurogenic, hormonal, thermal, topical, or other stimuli, has as its end

result an abnormal and persistent dilation of facial blood vessels.<sup>1,2,4-7</sup>

The regulation of the cutaneous circulation is of paramount importance and is extremely complex. It is mediated by the sympathetic nervous system both locally, through the release of catecholamines from the sympathetic nerve terminals, and systemically, through their release into the general circulation by the adrenal medulla. In recent years, and with newer molecular genetic techniques, the simple model of 2 adrenergic receptors (adrenoceptors) that mediate the vascular response to catecholamines<sup>8</sup> has been replaced. The concept of “generic”  $\alpha$ -adrenergic receptors, responsible mostly for “excitatory” functions such as vasoconstriction and uterine and urethral contraction, and “generic”  $\beta$ -adrenergic receptors, responsible mostly for “inhibitory” functions such as vasodilatation, bronchodilation, and uterine and urethral relaxation (though notably inotropic for the heart) has been further refined and specific receptor subtypes, localizations, and functions have been elucidated. The current model is that of a complex family of structurally related receptors consisting of at least 6  $\alpha$ -receptor subtypes ( $\alpha_{1A}$  [ $\alpha_{1a/c}$ ],  $\alpha_{1B}$ ,  $\alpha_{1D}$ ,  $\alpha_{2A}$  [ $\alpha_{2A/D}$ ],  $\alpha_{2B}$ , and  $\alpha_{2C}$ ) and at least 3  $\beta$ -receptor subtypes ( $\beta_1$ ,  $\beta_2$ , and  $\beta_3$ ),<sup>9-13</sup> with additional conformational variants such as  $\alpha_{1L}$  and  $\beta_4$  bringing the total number of functional adrenoceptor conformations to at least 11.

These adrenergic receptors are all members of the G-protein-coupled receptor superfamily of proteins and modulate their effects through a classic 7-transmembrane protein second-messenger system. Their final local and systemic effects, however, are myriad, as noted previously, including vasoactive effects ranging from vasoconstriction to vasodilatation, and occur through a wide variety of intracellular mechanisms<sup>12</sup> that are governed by local receptor subtype concentration, relative receptor subtype distribution throughout the body, ligand-binding characteristics, and other factors (eg, local temperature and hypoxia), the full discussion of which is beyond the scope of this article.<sup>9-14</sup> Elegant *in vitro*, *in vivo*, and *ex vivo* studies in a variety of vascular tissues and species reveal that the contraction of peripheral vascular smooth muscle is primarily mediated by  $\alpha_{1A}$ - and  $\alpha_{1D}$ -receptor subtypes, although it varies in different vas-

cular regions.<sup>10,11,15</sup> Studies of  $\alpha_2$ -receptor suggest that  $\alpha_{2A/D}$  and  $\alpha_{2B}$  effects are also of importance, particularly on the arterial side, and that the  $\alpha_{2A/D}$  and  $\alpha_{2C}$  effects are of importance on the venular side, although variations based on the experimental model used are well reported.<sup>10-13,15</sup> The actual physiologic and clinical responses to stimulating or inhibiting these receptors selectively is, however, difficult to predict.

Oxymetazoline is a synthetic, direct-acting, imidazoline-type sympathomimetic agonist that is highly selective for the  $\alpha_{1A}$ -adrenoceptor and is a partially selective  $\alpha_{2A}$ -receptor agonist as well. It is a potent vasoconstrictor. Locally applied  $\alpha_1$ -adrenoreceptor agonists such as phenylephrine hydrochloride, naphazoline hydrochloride, tetrahydrozoline hydrochloride, oxymetazoline hydrochloride, and xylometazoline hydrochloride are well known for their ability to clinically "get the red out" and have been used as vasoconstrictive agents in over-the-counter preparations for decades. These drugs have been used as decongestants on nasal and ocular mucous membranes for the treatment of conditions such as allergic rhinitis and conjunctivitis and decrease erythema and edema of the mucous membranes with safety and excellent efficacy. Selective  $\alpha_2$ -adrenoceptor agonists such as brimonidine tartrate and apraclonidine hydrochloride have similarly been applied to the ocular mucosa to take advantage of their vasoconstrictive (and other) actions to treat ocular hypertension and open-angle glaucoma, also with great efficacy. However, drugs of these classes have never been used for topical application to the skin.

Although it was initially believed that their effects were modulated purely through their vasoconstrictive properties, it has been demonstrated in recent years that several of the  $\alpha$ -adrenergic receptor vasoconstrictors also exhibit significant anti-inflammatory properties. In upper respiratory tract infections, oxymetazoline and xylometazoline have been shown to inhibit neutrophilic phagocytosis and oxidative burst, resulting in a decrease in microbial killing, decreased generation of proinflammatory cytokines, and decreased inflammation.<sup>16,17</sup> Oxymetazoline has also recently been shown to have significant effects on the arachidonic acid cascade, strongly inhibiting 5-lipoxygenase activity and thus decreasing the synthesis of the highly proinflammatory leukotriene B<sub>4</sub>.<sup>17</sup> A potential clinical role for oxymetazoline, or other agents of this class, as inhibitors of inflammation and oxidative-stress dependent reactions in inflammatory and/or infectious skin conditions is intriguing but has yet to be investigated.

Two major concerns of therapy with intranasal  $\alpha$ -agonist decongestants are those of a loss of efficacy with prolonged use due to desensitization (tachyphylaxis) and rebound vasodilation with a flare of erythema and edema. Neither of our patients exhibited either problem with the application of oxymetazoline to the skin. While the laboratory induction of receptor desensitization cannot yet be perfectly correlated with actual physiologic response, recent laboratory studies indicate that agonists that are more selective for  $\alpha_{1D}$ -adrenoceptors are less prone to induce receptor desensitization than are  $\alpha_{1A}$ - or  $\alpha_{1B}$ -agonists.<sup>18</sup> The clinical significance of this may be an important consideration in contemplating any potential future use of these drug classes on the skin because agonists

with certain receptor subtype binding profiles may retain their clinically desirable effects while minimizing their adverse effect.

In these 2 patients with treatment-resistant ETR rosacea, we report that topically administering a selective  $\alpha_1$ -agonist has resulted in a positive clinical response. This was evidenced as a durable improvement in the erythema, a marked decrease of erythematous flares, relief from the symptoms of stinging and burning, and no adverse effects. It seems plausible that the erythema and flushing of ETR may be due, at least in part, to an abnormal expression, function, distribution, or responsiveness of  $\alpha$ -adrenergic receptors, likely of an  $\alpha_1$ -receptor subtype, and that these clinical manifestations may be successfully treated by the topical application of agonists selective for  $\alpha_1$ -adrenergic receptors such as oxymetazoline.

Accepted for Publication: May 7, 2007.

Correspondence: Stuart D. Shanler, MD, 100 Winston Dr, Apt 17E North, Cliffside Park, NJ 07010 (sdsmd@aspectpharma.com).

Financial Disclosure: Drs Shanler and Ondo are principal owners and corporate officers in Aspect Pharmaceuticals LLC, Las Cruces, New Mexico, a privately held corporation that owns the rights to patent applications regarding the use of topically applied selective  $\alpha_1$ -agonists to the skin.

## REFERENCES

1. Crawford GH, Pelle MT, James WD. Rosacea, I: etiology, pathogenesis, and subtype classification. *J Am Acad Dermatol*. 2004;51(3):327-341.
2. Pelle MT, Crawford GH, James WD. Rosacea, II: therapy. *J Am Acad Dermatol*. 2004;51(4):499-512.
3. Wilkin J, Dahl M, Detmer M, et al. Standard classification of rosacea: report of the National Rosacea Society Expert Committee on the classification and staging of rosacea. *J Am Acad Dermatol*. 2002;46(4):584-587.
4. Plewig G, Kligman AM. *Acne and Rosacea*. 3rd ed. Berlin, Germany: Springer-Verlag; 2000:433-475.
5. Wilkin JK. Why is flushing limited to a mostly facial cutaneous distribution. *J Am Acad Dermatol*. 1988;19(2, pt 1):309-313.
6. Wilkin JK. Oral thermal-induced flushing in erythematotelangiectatic rosacea. *J Invest Dermatol*. 1981;76(1):15-18.
7. Parodi A, Guarrera M, Reboora A. Flushing in rosacea: an experimental approach. *Arch Dermatol Res*. 1980;269(3):269-273.
8. Ahlquist RP. A study of the adrenotropic receptors. *Am J Physiol*. 1948;153:586-600.
9. Kirstein SL, Insel PA. Autonomic nervous system pharmacogenomics: a progress report. *Pharmacol Rev*. 2004;56(1):31-52.
10. Piascik MT, Perez DM. Alpha1-adrenergic receptors: new insights and directions. *J Pharmacol Exp Ther*. 2001;298(2):403-410.
11. Civantos Calzada B, Aleixandre de Artinano A. Alpha-adrenoceptor subtypes. *Pharmacol Res*. 2001;44(3):195-208.
12. Guimarães S, Moura D. Vascular adrenoceptors: an update. *Pharmacol Rev*. 2001;53(2):319-356.
13. Hieble JP. Subclassification and nomenclature of alpha- and beta-adrenoceptors. *Curr Top Med Chem*. 2007;7(2):129-134.
14. Jarajapu YP, Johnston F, Berry C, et al. Functional characterization of alpha1-adrenoceptor subtypes in human subcutaneous resistance arteries. *J Pharmacol Exp Ther*. 2001;299(2):729-734.
15. Leech CJ, Faber JE. Different alpha-adrenoceptor subtypes mediate constriction of arterioles and venules. *Am J Physiol*. 1996;270(2, pt 2):H710-H722.
16. Bjerknes R, Steinsvag K. Inhibition of human neutrophil actin polymerization, phagocytosis, and oxidative burst by components of decongestive nose drops. *Pharmacol Toxicol*. 1993;73(1):41-45.
17. Beck-Speier I, Dayal N, Karg E, et al. Oxymetazoline inhibits proinflammatory reactions: effect on arachidonic acid-derived metabolite. *J Pharmacol Exp Ther*. 2006;316(2):843-851.
18. Chalothorn D, McCune DF, Edelman SE, et al. Differences in the cellular localization and agonist-mediated internalization properties of the alpha(1)-adrenoceptor subtypes. *Mol Pharmacol*. 2002;61(5):1008-1016.