Rosacea has traditionally been categorized into one of four subtypes: erythematotelangiectactic rosacea (ETR), papulopustular rosacea (PP), phymatous rosacea, and ocular rosacea. This system is inherently flawed, as patients may have disease overlapping more than one subtype at the same time. Since the introduction of this classification in 2002, newer recommendations have been published that move away from lumping patients into distinct buckets. The most recent consensus is to evaluate and treat patients based on symptoms. In 2016, a group of rosacea experts published recommendations as part of what was called the ROSCO (Global ROSacea COnsensus) panel. The group recommended that “persistent centrofacial redness associated with periodic intensification by potential trigger factors” be considered an independent diagnostic factor for rosacea. Inflammatory papules and pustules, flushing without persistent facial erythema, and telangiectasia were not considered sufficient for a diagnosis of rosacea by themselves, according to the ROSCO panel. (You can read more about the ROSCO panel in the February 2017 edition, available online at PracticalDermatology.com/2017/02.)

UNDERSTANDING FACIAL REDNESS
Facial redness is thought to be caused by neurovascular dysregulation, which leads both to an exaggerated flushing response as well as burning and stinging sensations. Aberrant vasodilation initially causes intermittent facial redness, but over time becomes fixed in the central face. Cutaneous vasodilation is primarily controlled through stimulation of $\alpha$-adrenoceptors. The primary receptor subtypes in the skin are $\alpha 1A$ receptor, found post-synaptically on smooth muscle of blood vessel walls, and the $\alpha 2$ receptor, which is expressed both in the pre-synaptic nerve terminal and in post-synaptic blood vessel smooth muscle. Activation of these receptors may have different effects in the skin.

TOPICAL TREATMENT OPTIONS
Currently, there are two FDA-approved drugs for the treatment of persistent facial erythema in rosacea. Topical brimonidine gel (Mirvaso, Galderma) is an $\alpha$-adrenergic agonist, thought to work on the $\alpha 2$ receptor. The recently approved oxymetazoline cream (Rhofade, Allergan) is an $\alpha$-adrenergic agonist selective for the $\alpha 1$ receptor. Binding to the adrenoreceptor leads to vasoconstriction of the cutaneous vasculature improving the background erythema in patients with rosacea. The two drugs bind to separate receptors explaining why activity in the skin is different.

In the phase 3 pivotal studies for oxymetazoline cream, 885 adult patients with moderate to severe facial erythema were randomized to receive active drug or vehicle. Patients were evaluated over a 29-day period, during which they applied the medication in the study center on days 1, 15, and 29. Between 94 percent and 98 percent of patients completed the study.

By the Numbers

Percentage of people with rosacea who are currently untreated, according to Wake Forest School of Medicine researchers, as reported by the National Rosacea Society (NRS; Rosacea.org). April was Rosacea Awareness Month.
Assessments were performed by both the investigator and the patients themselves over the course of 12 hours. Assessments were static, meaning that neither the investigator nor the patient could review what answers were given at earlier time points for reference. The assessment was made at each time period using a 5-point photographic scale as a reference.

The primary endpoint of the study was a 2-grade improvement in facial erythema, as assessed separately by the investigator and the patient at each time point on day 29 of the study. To be considered a success, both the investigator and the patient had to independently agree. Statistically significant improvements were seen in the active versus vehicle groups at each of the primary endpoint time points (hours 3, 6, 9, and 12). The drug was well tolerated, with the most common side effect being application site dermatitis, which was seen in two percent of patients in the active arm of the study.

Worsening of facial redness or a “rebound” effect has been found to be a significant issue in some patients using topical α-adrenoreceptor agonists. Post-marketing experience in patients using topical brimonidine gel revealed that up to 20 percent of patients reported transient worsening of erythema beyond their baseline level. This may manifest in different ways depending on the patient. Rebound may present as paradoxical reddening within a few hours of drug application or recurrence of redness that is worse than baseline after the drug wears off. Several theories explain this rebound effect. One theory is paradoxical vasodilation resulting from stimulation of the pre-synaptic α2-adrenoreceptor. This may be worsened by high amounts of the drug applied to the skin leading to over-saturation of receptors. Rebound may also be influenced by genetic polymorphisms.

Because of this rebound effect, worsening of erythema was specifically evaluated in the oxymetazoline studies. Following the 29-day active treatment arm in the pivotal studies, patients moved into a 28-day post-treatment follow-up period. During that time, there were no unscheduled visits or calls to the office regarding rebound erythema. In evaluating the post-treatment data, no clinically meaningful worsening of facial redness was detected. Similar data confirm a lack of clinically meaning rebound erythema in a safety study using oxymetazoline cream for 52 weeks, with a 14-day post-treatment follow-up period.

**TARGETING REDNESS**

While most of our medical rosacea treatments previously targeted papules and pustules, we now have new, safe medical options that address persistent facial erythema. Facial redness is the unifying factor among almost all rosacea patients and bears a significant burden on quality of life.

With new options in our tool belts, we can decide which drugs and which drug combinations best serve the needs of each individual patient.

Disclosures: Dr. Zeichner has served as a consultant, advisory board member, or speaker for Allergan, Bayer, and Galderma.

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