Rosacea Therapy: Current Approaches and Future Directions

By Joseph Bikowski, MD

There is, of course, no cure for erythematotelangiectatic rosacea (ETR), but over the past several years, patients and physicians have seen advancements in therapy, leading to improved outcomes and enhanced treatment tolerability. Furthermore, research showing that treatment can improve the quality of life of patients affected by rosacea has highlighted the importance of diagnosing rosacea effectively and offering patients efficient therapeutic options.

One of the greatest therapeutic challenges for clinicians is that rosacea is a chronic disease in which an altered innate immune response is just one aspect of the complicated pathophysiology. Resultant chronic inflammation yields a constellation of presenting symptoms, the quality and degree of which varies from one patient to another. No single agent can address the multiple causes and resultant symptoms of rosacea, but new developments suggest that emerging options may allow clinicians to optimize outcomes through combination drug therapy.

Current Treatments

The agents most frequently used in the management of ETR include topical metronidazole, topical azelaic acid, sodium sulfacetamide-sulfur, and anti-inflammatory dose doxycycline 40mg. These agents are shown to produce a reduction in papules and pustules and to possibly improve the appearance of facial erythema. In conjunction with proper skin care, treatment may be associated with improvements in skin texture.

Azelaic acid (Finacea gel 15%, Intendis) is well-tolerated in the management of rosacea and may help to preserve barrier function. In a two-week trial, women with rosacea who applied the gel twice-daily had no evidence of barrier damage on TEWL or corneometry tests. Of note, the 15% gel formulation provides an eight-fold increase in the delivery of azelaic acid compared to azelaic acid cream 20%. This is likely because the gel contains some solubilized azelaic acid, whereas the cream does not.

Metronidazole (MetroGel 1%, Galderma), a recent update of the originally approved topical metronidazole formulation, features hydrosolubilizing agent (HSA), a cyclodextran ring in which metronidazole resides. Unlike metronidazole, HSA is readily dissolved in the aqueous gel vehicle, permitting an even dispersion of the high concentration of topical metronidazole.

Anti-inflammatory dose doxycycline (Oracea, Galderma) has become a first-line oral agent for the management of rosacea. The novel formulation, containing both immediate- and delayed-release doxycycline, enables plasma concentrations of doxycycline to peak well below the minimal inhibitory concentration (MIC) for the drug and thus obviates concerns about the development of resistance. In clinical trials, patients using anti-inflammatory dose doxycycline experienced notable clearance of inflammatory lesions and background erythema with a low incidence of adverse events.

Rosacea Mimickers

Efficient treatment of rosacea requires accurate diagnosis, so keep rosacea mimickers in mind. See the December edition online at PracticalDermatology.com for details:

- Demodex Dermatitis
- Folliculitis
- Perioral Dermatitis
- Pseudorhinophyma
Despite the efficacy of topical and/or systemic therapies to calm the inflammation associated with rosacea, reduce the number of inflammatory lesions, and thereby reduce some of the erythema associated with rosacea, no pharmacologic agent is primarily effective for redness reduction. New topical prescription formulations in development are targeting redness.

**REDNESS REDUCERS IN THE PIPELINE**

Topical agents to reduce the appearance of diffuse erythema are in development and may be available on the market soon (Table). CD07805/47 or brimonidine tartrate gel (BT) is a proprietary topical gel that Galderma is investigating for the treatment of moderate-to-severe facial erythema in adults with rosacea. Two randomized, vehicle-controlled, multicenter Phase III trials that investigated the efficacy and safety of CD07805/47 applied topically once daily vs. vehicle in adult patients with moderate-to-severe facial erythema of rosacea have been completed. Galderma reports that results of the Phase III trials were consistent with results of Phase II trials, published earlier this year.10

In the first of the Phase II trials,10 a total of 122 subjects were randomized to receive a single application of BT gel 0.07%, 0.18%, 0.5%, or vehicle. In the second Phase II trial, 269 subjects were randomized to receive BT 0.5% once daily, BT 0.18% once daily, vehicle once daily, BT 0.18% twice daily, or vehicle twice daily. Evaluations included Clinician’s Erythema Assessment (CEA), Patient’s Self-Assessment (PSA), Chromameter measurements, and adverse events.

Analysis of the first trial data showed that a single application of topical BT gel reduced facial erythema in a dose-dependent fashion. There was a significant difference in redness value (as measured by Chromameter) between BT 0.5% and vehicle from 30 minutes to 12 hours after application.

The second trial showed that BT gel 0.5% once daily had a statistically superior success profile (defined as a two-grade improvement on both CEA and PSA over 12 hours) compared with vehicle once daily on days 1, 15, and 29 (all P < 0.001). No tachyphylaxis, rebound of erythema, or aggravation of other disease signs (i.e., telangiectasia, inflammatory lesions) was observed.

Brimonidine tartrate is a selective alpha 2-adrenoceptor agonist currently used in an ophthalmic solution for the management of open-angle glaucoma and ocular hypertension.11 Its vasoconstrictive properties presumably contribute to the reduction in erythema of rosacea.

Another topical anti-redness agent, AGN-199201 or oxymetazoline, is a selective alpha-1 agonist and partial alpha-2 agonist currently used as a topically applied nasal decongestant. Allergan acquired the agent from Vicept Therapeutics after promising Phase II studies were completed.

Although results of those trials have not been published, there is evidence in the literature that topically applied oxymetazoline reduces the erythema of rosacea.12 A series of case reports involved application of the currently marketed nasal spray to the skin of rosacea patients. AGN-199201 is a cream formulation developed specifically for use by rosacea patients.

**LOOKING AHEAD**

Currently, meaningful reduction of erythema in rosacea requires the use of lasers. While lasers will probably continue to provide the most persistent reduction in erythema and represent the most effective intervention for telangiectases, the topical prescription redness-reducers in development would be a welcome addition to the treatment field. If these agents come to market, they may become important tools for reducing the cosmetic impact and quality of life impairment associated with rosacea.

---

**TABLE. A CLOSER LOOK AT THE PIPELINE**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Developed by</th>
<th>Mode of action</th>
<th>Current indication/use</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD07805/47 or brimonidine tartrate gel</td>
<td>Galderma</td>
<td>alpha-2 adrenergic agonist</td>
<td>Ophthalmal solution for reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension</td>
</tr>
<tr>
<td>Oxymetazoline</td>
<td>Allergan</td>
<td>alpha-1 agonist and partial alpha-2 agonist</td>
<td>Nasal spray for reduction of nasal decongestion</td>
</tr>
</tbody>
</table>

---