Oracea Is Promising Nonantibiotic Tx for Rosacea

Conventional antibiotics work well for rosacea, but it is not caused by bacteria.

BY BRUCE JANCIN
Denver Bureau

KOLOA, HAWAII — With marketing approval of the anti-inflammatory, nonantibiotic formulation of doxycycline for treatment of rosacea widely anticipated by the end of May, this new once-daily oral medication is likely to be viewed as the best therapeutic option for patients with papulopustular forms of the disease, Dr. Hilary E. Baldwin said at the annual Hawaii dermatology seminar sponsored by the Skin Disease Education Foundation.

It has long been recognized that conventional antibiotics—particularly those in the tetracycline class—are highly effective in rosacea, even though it is now clear that the disease isn't actually caused by bacteria.

However, long-term use of antimicrobials to treat a chronic disease such as rosacea, which may last for decades, is increasingly seen as irresponsible because it contributes to the rise of antibiotic-resistant, highly pathogenic bacteria.

"This is not a minor problem. It's not something that people are making up. It's a truly global-impact problem. And by treating a nonbacterial disease with antibiotics, we're adding to the problem," stressed Dr. Baldwin of the State University of New York, Brooklyn.

Fortunately, physicians have access to a range of nonantibiotic alternatives in treating rosacea. The best of them could be Oracea: Its once-daily formulation of doxycycline is far cheaper than lasers, devoid of the teratogenicity concerns posed by oral and topical retinoids, and far more effective than β-blockers and other antiflushing medications, she said.

Here's a rundown of the nonantibiotic options for rosacea:

▶ **Oracea.** Food and Drug Administration approval is anticipated for this agent as a 40-mg controlled-release drug indicated for treatment of rosacea. Its big selling point—in addition to the efficacy—is that this dose lies below the drug's threshold of antibiotic activity. Hence, there are no concerns regarding the emergence of bacterial resistance.

In two double-blind, placebo-controlled, phase III trials, 537 rosacea patients were randomized to Oracea or placebo once daily for 16 weeks. Patients on Oracea experienced mean reductions in inflammatory lesion count of 61% and 46%, compared with 29% and 20%, respectively, for placebo.

The drug's mechanisms of benefit in rosacea are believed to involve four processes: inhibition of neutrophil-derived serum matrix metalloproteinases, down-regulation of inflammatory cytokines, inhibition of nitric oxide activity as well as that of other reactive oxygen species, and suppression of the arachidonic acid pathway.

In addition, Oracea inhibits collagenase activity, which is increased in rosacea and is thought to be a cause of the dystrophic dermal connective tissue that's a disease hallmark, the dermatologist continued.

▶ **Topical retinoids.** These are highly effective for rosacea but have never really caught on, partly because clinical improvement isn't seen until after 2-3 months. Most patients don't want to wait that long.

'By treating a nonbacterial disease with antibiotics, we're adding to the problem.'

DR. BALDWIN

"You can certainly add a topical retinoid at the initiation of therapy along with something that gives you a bit more bang for the buck in the first couple of weeks, then back off to the use of the retinoid alone as it starts to become effective," Dr. Baldwin said.

Although the conventional wisdom has been that topical retinoids shouldn't be used in rosacea because they'll cause patients' skin to become even more red due to angiogenesis, that's not true, she said.

"If you start with a particularly low-dose retinoid like tretinoin 0.05% cream, or start with adapalene and build up, or if you use silicone-based moisturizers under the topical retinoid, most patients can actually tolerate the treatment just fine," she continued. "The problem, of course, is that these drugs are category C or X in pregnancy, and that's an issue in women of childbearing potential."

▶ **Isotretinoin.** This also has a delayed onset of action and teratogenicity issues.

The oral retinoid decreases papules, pustules, and erythema. It also will modestly decrease the volume of existing rhinophyma by reducing the size and number of sebaceous glands, "but it works even better to prevent the accelerating process of phyma formation. If you have a patient whose phyma is sort of galloping ahead, this is one of your options for treatment. It also improves ocular disease," Dr. Baldwin said.

"And if you use it long term and low dose, you have very few side effects," she added.

Dr. Baldwin also noted that isotretinoin in combination with a topical retinoid works better than either alone.

▶ **Antiflushing drugs.** There are plenty of favorable case reports involving β-blockers, clonidine, and, more recently, the selective serotonin reuptake inhibitors, yet "in most of our hands none of these has worked very well," she said.

Complete control of flushing using propranolol, for example, seems to require dosing at 20-40 mg b.i.d. or t.i.d., and the side effects are considerable at those levels.

▶ **Lasers and light-based therapy.** These excel where pharmacotherapy is weakest: rosacea involving severe erythema and telangiectasias. In addition, the CO_2 and other ablative lasers are highly useful for removal of rhinophymas and prevention of recurrences, Dr. Baldwin said.

Vascular lasers make a great deal of sense for erythematous/telangiectatic forms of rosacea because they cause vascular destruction without collateral tissue damage.

Polychromatic light of multiple wavelengths from yellow to infrared has been used with great success in rosacea. Large areas are easily treated using this method.

This form of therapy doesn't result in purpura, and patients are quite happy with the results, but a good deal of individual tailoring is required to target multiple chromophores at different skin depths, she explained.

Photodynamic therapy with either a polychromatic or monochromatic light source along with a photosensitizing agent preferentially targets sebaceous glands, but treats papulopustular forms of rosacea as well—and offers the side benefit of improved skin quality.

Erbium:YAG lasers and nonablative lasers are believed to work in rosacea by inducing proliferation of fibroblasts and endothelial cells, Dr. Baldwin said.

She is a consultant to Colla-Genex Pharmaceuticals Inc., which is developing Oracea.

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New MetroGel Formulation Offers Advantages in Rosacea

BY BRUCE JANCIN
Denver Bureau

KOLOA, HAWAII — The metronidazole gel 1% approved by the Food and Drug Administration last year for the treatment of rosacea is a better product in two distinct ways than the 0.75% preparation it replaces, Dr. Guy F. Webster said at the annual Hawaii dermatology seminar sponsored by the Skin Disease Education Foundation.

The new version incorporates a higher concentration of metronidazole, of course, but it also utilizes a new water-based, alcohol-free vehicle that's much gentler on the skin of atopic dermatitis patients. Indeed, patch test studies have shown that metronidazole gel 1% (MetroGel) has a very low potential for irritation. "It's clearly beneficial as a moisturizer, let alone as an anti-inflammatory drug," said Dr. Webster of Jefferson Medical College, Philadelphia.

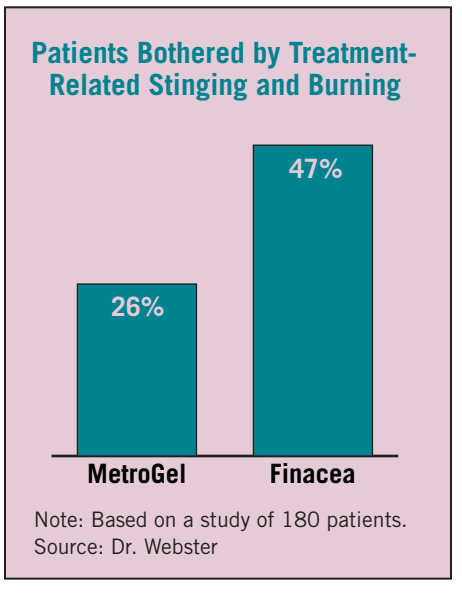
The pivotal phase III clinical trial that led to FDA approval last year involved 746 rosacea patients randomized 3:1 to 10 weeks of once-daily MetroGel or its gel vehicle.

At 10 weeks, the mean inflammatory lesion count—18 lesions at baseline—was reduced by 51% in the MetroGel group and by 33% in controls.

In addition, 38% of the MetroGel group were rated by investigators' global assessment as clear or almost clear and 29% as unchanged, compared with 28% and 41%, respectively, of controls.

In a separate phase IIIb clinical trial, MetroGel significantly outperformed azelaic acid gel 15% (Finacea) in terms of tolerability. The investigator-blinded multicenter study involved 180 rosacea patients randomized to 15 weeks of once-daily MetroGel or twice-daily Finacea.

The two treatments showed equal efficacy in terms of reductions in inflammatory lesions, erythema, and physicians' global severity scores; however, only 26% of patients in the MetroGel group indicated they were bothered by stinging and burning, compared with 47% on Finacea.



Dr. Webster deemed the cost of once-daily MetroGel reasonable at slightly under $1 per day.

A potential topical therapy for rosacea worth keeping an eye on is dapsone gel 5% (Aczone), he said. It received FDA marketing approval last year for acne vulgaris, but its manufacturer, QLT Inc., has decided to delay the drug's launch until after completion of an ongoing phase IV study aimed at getting the FDA's requirement for patient blood tests removed. Meanwhile, a phase II study of Aczone for the treatment of rosacea is ongoing.

Based on Aczone's pharmacokinetics, Dr. Webster said the FDA's restriction was likely to be lifted upon presentation of additional data by QLT.

He is a consultant to Galderma, which markets MetroGel, but is not involved in the Aczone trials.

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