Oracea Called Best Nonantibiotic for Rosacea

Pending its approval, this drug will be added to the list of therapies that don't contribute to resistance.

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 this month, this new once-daily oral agent 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 are the nonantibiotic alternatives:

▶ **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 inhibition of neutrophil-derived serum matrix metalloproteinases, downregulation 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.

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

She added 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 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.

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

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.

Add a topical retinoid at the initiation of therapy along with something that gives a bit more bang for the buck.

DR. BALDWIN

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 CollaGenex Pharmaceuticals Inc., which is developing Oracea.

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Anti-Inflammatory Doxycycline Clears Rosacea Lesions

BY JANE SALODOF MACNEIL
Southwest Bureau

KAPALUA, HAWAII — A formulation of doxycycline that is anti-inflammatory without being antibiotic significantly reduced rosacea lesions in two phase III trials, according to Dr. James Q. Del Rosso, the principal investigator.

Dr. Del Rosso, a dermatologist in Las Vegas, reported that CollaGenex Pharmaceuticals Inc., in Newtown, Pa., for which he works in several roles, has applied to the Food and Drug Administration for an indication in rosacea based on the outcomes.

He gave a general description of the findings at the Winter Clinical Dermatology Conference, Hawaii, and said that data from the trials would be presented at the American Academy of Dermatology meeting this month. "This therapy provides the anti-inflammatory effect but does not predispose patients to development of antibiotic resistance. That is significant," he said in an interview.

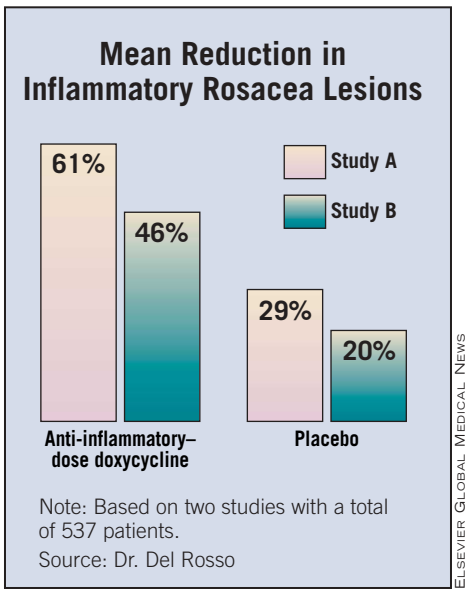
In his presentation, he suggested that antibiotic resistance was a concern because rosacea is a chronic disease for which patients are often treated for long periods. All tetracyclines have anti-inflammatory activity, he said, but doxycycline is the only one for which investigators have separated anti-inflammatory from antibiotic dosing.

This therapy is anti-inflammatory but does not predispose patients to antibiotic resistance.

DR. DEL ROSSO

Anti-inflammatory–dose doxycycline is a 40-mg, controlled-release doxycycline monohydrate capsule that is administered once a day, said Dr. Del Rosso. "The advantage of once-daily dosing is obviously better patient compliance," he added.

All told, 537 patients at 28 sites were enrolled in the two randomized, double-blind, placebo-controlled studies. The investigator said that patients in both trials achieved significant improvements in inflammatory lesion counts and in Investigator's Global Assessment of Improvement scores with anti-inflammatory–dose doxycycline.



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"In the two studies, patients receiving anti-inflammatory–dose doxycycline experienced a 61% and 46% mean reduction in inflammatory lesions, compared to 29% and 20%, respectively, in those receiving placebo," Dr. Del Rosso said. Lesion-count drops in the doxycycline group became statistically significant as early as 3 weeks after treatment began.

Erythema also improved progressively in both trials, with one trial demonstrating a statistically significant difference from placebo, he said at the conference, which was sponsored by the Center for Bio-Medical Communication Inc.

Adverse reactions were similar in the placebo and active groups in both studies.

Neither trial reported phototoxicity or photosensitivity, and no female patients developed oral or vaginal candidiasis during treatment with anti-inflammatory–dose doxycycline, he emphasized. ■