Inflammation in Acne, Rosacea Responds to Low-Dose Antibiotics

Low doses of doxycycline and some other antibiotics have antiinflammatory effects that have promise in the management of acne and rosacea and perhaps other disorders as well, according to Philadelphia dermatologist, Guy Webster, MD, PhD.

When doxycycline and some other antibiotics are used in doses under minimum inhibitory concentrations (MICs), they have no detectable effect on growth of the bacteria. Thus, they do not pose any risk for development of bacterial resistance with long-term use. Despite the fact that sub-MIC doses of some antibiotics do not affect floral growth, they do inhibit the bacteria from producing such proinflammatory products as neutrophil chemotactic factor, said Dr. Webster, Professor and Vice-Chairman of the Department of Dermatology at Thomas Jefferson University School of Medicine.

In addition, sub-MIC doses of doxycycline and certain other antibiotics do not cause the adverse side effects seen with potent immunosuppressants such as cyclosporine. It does not take a potent immunosuppressant to manage acne and rosacea; these are relatively mild inflammatory diseases that respond to medication with mild antiinflammatory effects.

Dr. Webster stressed the difference between a subtherapeutic dose and a sub-MIC or subantimicrobial dose. An antibiotic that is given in a subtherapeutic dose can still be above the MIC and thus increase the risk for development of bacterial resistance. When antibiotics are given in sub-MIC doses, there is no selective pressure for resistant organisms. Because there is no antimicrobial activity, resistance cannot be induced.

The Antiinflammatory Properties of Antibiotics

Antibiotics are not the first class of drugs to be used for more than one effect. The antimalarial drug hydroxychloroquine has been shown to kill plasmodia and lessen the symptoms of both lupus and sarcoidosis. Aspirin not only relieves pain, it inhibits platelets and lowers fever.

Dapsone began its clinically useful life as one of the first antiinfectious agents but is only occasionally used for its bactericidal properties. Instead, physicians use it for its antiinflammatory effects, which are associated with its inhibitory effect on neutrophil activity. Dapsone has not been equally effective in all neutrophil-rich diseases. The drug works best in dermatitis herpetiformis and linear IgA bullous dermatosis. Dapsone works moderately well in psoriasis, granulomatosis with polyangiitis, and catarrhal pemphigoid. It works in dermatitis herpetiformis and linear IgA bullous dermatosis.

When doxycycline and some other antibiotics are used in doses under minimum inhibitory concentrations, they have no detectable effect on growth of the bacteria. These drugs are effective in treating lichen planus pilaris and some other scalp inflammations. “Although infectious processes aren’t involved in these scalp inflammations, the sulfonamides do some good,” he said. Tetracyclines in particular are very effective antiinflammatory drugs that lessen inflammation by a number of mechanisms. They inhibit nitric oxide, which modulates blood flow and white blood cell function, especially in wound healing and inflammation. Tetracyclines have been shown to be protective against cardiovascular disease by inhibiting nitric oxide generation (Proc Nat Acad Sci USA. 1998; 95:15769-15774). In addition, tetracyclines have been shown to decrease inflammatory bone marrow suppression, and neuropathy, which are common adverse effects associated with dapsone use, according to Dr. Webster.

Sulfonamides also have a proven track record as antiinflammatory agents. The combination of trimethoprim and sulfamethoxazole (TMP/SMX) has been shown to effectively treat mild Wegener’s granulomatosis (Arch Intern Med. 1991;151:1649-1652). Dr. Webster noted that sulfonamides are used effectively in dermatology as antiinflammatory agents. These drugs are effective in treating lichen planus pilaris and some other scalp inflammations. “Although infectious processes aren’t involved in these scalp inflammations, the sulfonamides do some good,” he said. Tetracyclines in particular are very effective antiinflammatory drugs that lessen inflammation by a number of mechanisms. They inhibit nitric oxide, which modulates blood flow and white blood cell function, especially in wound healing and inflammation. Tetracyclines have been shown to be protective against cardiovascular disease by inhibiting nitric oxide generation (Proc Nat Acad Sci USA. 1998; 95:15769-15774). In addition, tetracyclines have been shown to decrease inflammatory bone marrow suppression, and neuropathy, which are common adverse effects associated with dapsone use, according to Dr. Webster.

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Adverse Side Effects Rare with Subantimicrobial Doses of Some Antibiotics

Joseph F. Fowler, Jr, MD

Subantimicrobial-dose (SD) doxycycline is probably no more or less effective than a standard dose but would be in reducing inflammatory skin lesions seen with acne and rosacea. The advantage offered by the low-dose regimen is a complete absence of the adverse side effects that one expects men is a complete absence of the side effects that physicians expect to see with this antibiotic, reports Louisville, Kentucky dermatologist, Joseph F. Fowler, Jr., MD.

Acne

The lack of adverse side effects was seen in a study of SD doxycycline that was conducted by Robert A. Skidmore, Jr., MD, at University of Florida in Gainesville, where he is Medical Director of the SHANDS Dermatology & Skin Cancer Center. A total of 59 people with acne who were enrolled in the multicenter study. They were randomized to receive either a twice-daily 20-mg dose of oral doxycycline or placebo. Participants were not allowed to use any other prescription or over-the-counter product for their acne during this 6-month study, according to Dr. Fowler, who is Clinical Professor of Dermatology at the University of Louisville School of Medicine.

The average age of the participants was 23 years (range, 18 to 37 years), and 40 (67.8%) were Caucasian. There were 32 females in the study. A total of 40 individuals completed the study, and they were equally divided between those on SD doxycycline and those on placebo.

Doxycycline’s Antiinflammatory Effects in Acne

SD doxycycline was significantly more effective than placebo at reducing the number of inflammatory acne lesions (pustules and papules) in treated patients, said Dr. Fowler, in reporting the unpublished data. SD doxycycline was also significantly more effective than placebo at reducing the number of comedones. At the end of 6 months, there was a 50.1% reduction in inflammatory lesions in the subjects on doxycycline versus a 30.2% reduction in those on placebo. There was a 53.6% reduction in comedones with SD doxycycline treatment versus a 10.6% decrease with placebo. Overall, the combined number of comedones and inflammatory lesions decreased by 52.3% in patients taking SD doxycycline and by 17.5% in those on placebo (Figure).

Data from examinations conducted at 2 months and 4 months show that there was a trend toward greater improvement in patients taking SD doxycycline, but the difference did not become statistically significant until 6 months. “We all know that normally acne tends to get a little better and a little worse over the course of 6 months...[I]n the doxycycline group, there was a steady improvement manifested by the downward counts of both comedones and inflammatory lesions,” Dr. Fowler said.

The subantimicrobial-dose of doxycycline that investigators used in this study did not produce any of the side effects that physicians expect to see with antibiotic therapy. “We all know that many times systemic antibiotic therapy can lead to gastrointestinal discomfort, upset stomach, diarrhea, photosensitivity, and yeast infections in women,” noted Dr. Fowler. However, the rates of side effects were comparable between the two treatment groups.

Continued on page 4
Rosacea Inflammation Controlled With Novel Monotherapy

Doxycycline given in a subantimicrobial dose can significantly lessen the inflammation of rosacea both when used in combination with metronidazole and when continued as maintenance monotherapy, according to Jorge L. Sánchez, MD.

Rosacea is an inflammatory process that involves primarily the central aspect of the face: the cheeks, chin, nose, and forehead. Rosacea is marked by recurrent episodes of blushing, erythema, edema, papules, pustules, and, later, fibrosis. Onset is usually after middle age; men and women are affected in equal numbers, as are Caucasians, African Americans, and Asians.

Standard therapy for mild rosacea is topical metronidazole, topical sulfacetamide, or topical azelaic acid. For moderate rosacea, the usual therapy is topical metronidazole, topical antibiotics, or systemic antibiotics. Patients with more advanced rosacea usually receive short courses of oral metronidazole or metronidazole plus doxycycline.

In a double-blind phase III study, 40 patients with moderate rosacea were randomized to receive one of two treatment regimens: They took either 20 mg of oral subantimicrobial-dose (SD) doxycycline twice a day in combination with 0.75% topical metronidazole or placebo plus metronidazole for 12 weeks. Thereafter, the metronidazole was discontinued; patients continued to take either SD doxycycline or placebo for another 4 weeks, said Dr. Sánchez, Professor and Chairman of the Department of Dermatology at the University of Puerto Rico School of Medicine in San Juan and the study’s principal investigator.

The people who participated in the study were all otherwise healthy men and women with rosacea. Specifically, they had 8 to 30 papules and/or pustules and no more than two nodules. Their erythema was moderate to severe with a minimum score of 2 on an ordinal scale of 5. All the people in the study had telangiectasia.

Subjects were asked to not use any other prescription or over-the-counter treatment for rosacea or acne for the duration of the study. Women of childbearing potential in the study were required to use contraception.

The number of total inflammatory lesions decreased in both treatment groups over the first 12 weeks of the study, but the decline was significantly greater in the patients taking the combination of SD doxycycline and metronidazole than in those on placebo and metronidazole. By the fourth week of the study, the total number of inflammatory lesions in the group on SD doxycycline plus metronidazole had decreased by a mean of 38% versus 19% in the group on placebo and metronidazole. By week 12, the total number of inflammatory lesions had decreased by a mean of 64% in the SD doxycycline/metronidazole-treated group versus 44% in the placebo/metronidazole-treated group, said Dr. Sánchez, reporting the unpublished data.

The global erythema score also decreased significantly more in the subjects treated with SD doxycycline and metronidazole than in those treated with placebo and metronidazole. By the fourth week of the study, the score had decreased by a mean of 12% in both groups. By the end of the 12th week, the mean score had decreased by 22% in the SD doxycycline/metronidazole group and 13% in the placebo/metronidazole group.

All these measures continued to show more improvement between weeks 12 and 16 in the subjects receiving maintenance monotherapy with SD doxycycline than in those on placebo. Between the 12th and 16th weeks of the study, the mean total number of inflammatory lesions decreased by a further 9% in the individuals on SD doxycycline but increased by 2% in those on placebo. The global erythema score decreased by a further 7% in the subjects taking SD doxycycline monotherapy, compared to 4% in those on placebo, reported Dr. Sánchez.

The patients on the subantimicrobial dose of doxycycline did not develop nausea, vomiting, headaches, photosensitivity, or yeast vaginitis. Overall, the rate of side effects was similar in both groups [Table], according to Dr. Sánchez.

<table>
<thead>
<tr>
<th>Table. Most Frequent Treatment-Emergent Adverse Events</th>
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<tr>
<td><strong>Adverse Events</strong></td>
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<tr>
<td><strong>Contact irritation</strong></td>
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<tr>
<td><strong>Nausea</strong></td>
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<td><strong>Headache</strong></td>
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**SOURCE: Dr. Jorge L. Sánchez.**

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**Inflammation in Acne**

Continued from page 1

Inflammation, which may be caused by bacteria, plugs a follicle to form a comedo. Formation of a comedo is not an inflammatory process. And, in some patients, comedones never evolve into anything else.

In other patients, the onset of sebaceous secretions inflates the impacted follicle and provides nutrition for Propionibacterium acnes, which triggers the inflammation in some patients. At-risk individuals are those who develop immune hypersensitivity to P. acnes and its products; as a result, they develop inflammatory acne lesions. P. acnes activates both classical and alternative inflammation pathways. It stimulates generation of neutrophil chemotactic factors, mostly CSF. In addition, P. acnes triggers both release of neutrophil lysosomes and synthesis of proinflammatory molecules. P. acnes is a persistent microbe that causes persistent inflammation.

This bacterium degrades very slowly. As a result, P. acnes stays within reach of the immune system for a long time because inflammatory cells cannot break it down (J Am Acad Dermatol. 1995;33:247-253).

Inflammation in Rosacea

Not all rosacea is inflammatory and they all kill P. acnes, according to Dr. Webster.

Likewise, the mite demodex has been wrongly implicated in the pathophysiology of rosacea. Rosacea does not improve when patients are treated with lindane, which kills demodex, he added. The antibiotics that can be used effectively as antiinflammatory agents against rosacea are the tetracyclines, ciprofloxacin, TMP/SMX, and metronidazole. These drugs are all directly antiinflammatory and they all kill P. acnes, he said [Table, page 1].
**Adverse Side Effects Continued from page 2**

The lack of increased photosensitivity in the doxycycline-treated patients is particularly remarkable, given that most of the individuals who participated in the study were sun-loving college students living in Florida. “A lot of these youngsters undoubtedly were out in the sun more than they should have been. Despite that, there was no photosensitivity noted,” he said.

One woman had slightly lower hemoglobin and hematocrit values on doxycycline, findings that were probably related to her menstrual period. Two individuals, both on placebo, had elevated liver function tests, which were probably the result of alcohol consumption by these college students.

A comparison of microbiologic studies of skin specimens taken from the center of the brow at baseline and again after 6 months of treatment showed that doxycycline given in substantimicrobial doses had no effect on the composition or prevalence of skin flora. In particular, there was no decrease in numbers of *Propionibacterium acnes*. Nor was there any effect on the resistance profile of the bacteria that were present on the skin. Resistance testing done on cultures of the microbes found in the skin specimens showed that, despite 6 months of SD doxycycline therapy, resistance did not develop to doxycycline, other tetracyclines, and other common antibiotics.

**Rosacea**

Rosacea is primarily an inflammatory condition. Patients with rosacea stand to benefit greatly from a treatment that could both reduce the inflammation and not impose any adverse side effects.

Dr. Fowler reported that low-dose doxycycline was shown to be effective and safe in an open-label observation study done by Joseph Bikowski, MD, Assistant Clinical Professor of Dermatology at the University of Pittsburgh (Skin Med. 2003;2:4:234-245). He enrolled 50 patients with mild, moderate, or severe rosacea who received monotherapy with 20 mg of doxycycline given twice daily for 8 weeks.

**Perioral Dermatitis**

Although this condition is labeled as a dermatitis, it is more of an acneiform eruption that occurs following prolonged use of topical corticosteroids. Topical corticosteroids also are used to treat it, and that approach has been effective. However, when corticosteroids are withdrawn, the perioral dermatitis can return, sometimes worse than before. Some occlusive makeup products, facial moisturizers, and fluorescent toothpaste exacerbate the condition.

There have been anecdotal reports that therapeutic doses of systemic doxycycline or other tetracyclines have cleared up co-existing perioral dermatitis when given for other indications. Two investigators who are collaborating on the design of this multicenter phase III trial are Mark Lebwohl, MD, of Mount Sinai Hospital in New York, and Ruby Ghadially, MD, of the University of California at San Francisco, according to Dr. Fowler.

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**The Treatment of Acne Vulgaris and Rosacea: A Novel Approach**

**CME Post-Test and Evaluation**

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**INSTRUCTIONS:** For each question or incomplete statement, one answer or completion is correct. Four of six correct responses are required for credit. Circle the most appropriate response.

1. Doxycycline 20 mg BID has been shown to:
   a. Allow overgrowth of certain skin bacteria.
   b. Have no effect on the composition of skin flora.
   c. Select out resistant strains of *Propionibacterium acnes*.
   d. Change resistance of skin flora to other tetracyclines.
   
2. Which of the following statements about rosacea is not true?
   a. Rosacea is an anti-inflammatory process.
   b. The disease process involves recurrent episodes of blushing, erythema, edema, papules, pustules, and, later, fibrosis.
   c. The disease is more common among Caucasians.
   d. The disease involves primarily the central aspect of the face.
   
3. Perioral dermatitis is an acneiform eruption that results from:
   a. Prolonged use of topical steroids
   b. Makeup
   c. Immunodeficiency
   d. Eating greasy foods
   
4. Doxycycline 20 mg BID is an effective treatment for moderate rosacea when used as which of the below?
   a. Combination therapy with topical metronidazole
   b. Maintenance monotherapy
   c. Both of the above
   d. None of the above
   
5. The most potent antiinflammatory antibiotic, as measured by protein kinase C, is:
   a. Minocycline
   b. Ciprofloxacin
   c. Pentoxifylline
   d. Doxycycline
   
6. Which of the following antibiotics are useful for their antiinflammatory properties in treating skin diseases?
   a. Dapsone
   b. TMP/SMX
   c. Low-dose doxycycline
   d. All of the above
   e. None of the above
   
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**Post-Test**

**Figures/Tables**

**Text**

1. How would you rate the clarity of the presentation of the material? (Please check one)
   a. Excellent
   b. Good
   c. Fair
   d. Poor

2. How would you rate the clinical relevance of the material? (Please check one)
   a. Excellent
   b. Good
   c. Fair
   d. Poor

3. How would you rate this material, compared with similar independent study presentations in print form? (Please check one)
   a. Excellent
   b. Good
   c. Fair
   d. Poor

4. Was this a fair and balanced presentation? Please comment on the scientific rigor, fairness, and balance of the material.

5. Do you believe such materials, supported by educational grants from industry, are appropriate and useful? Please rate from 0 (not appropriate/useful) to 10 (very appropriate/useful).

6. What topics would you find useful for future programs?

7. Other comments:

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**Signature**

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