ORIGINAL ARTICLE

Improved clinical outcome and biomarkers in adults with papulopustular rosacea treated with doxycycline modified-release capsules in a randomized trial

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Background: Patients with rosacea have increased amounts of cathelicidin and protease activity but their usefulness as disease biomarkers is unclear.

Objective: We sought to evaluate the effect of doxycycline treatment on cathelicidin expression, protease activity, and clinical response in rosacea.

Methods: In all, 170 adults with papulopustular rosacea were treated for 12 weeks with doxycycline 40-mg modified-release capsules or placebo in a multicenter, randomized, double-blind, placebo-controlled study. Clinical response was compared with cathelicidin and protease activity in stratum corneum samples obtained by tape strip and in skin biopsy specimens obtained from a random subset of patients.

Results: Treatment with doxycycline significantly reduced inflammatory lesions and improved investigator global assessment scores compared with placebo. Cathelicidin expression and protein levels decreased over the course of 12 weeks in patients treated with doxycycline. Low levels of protease activity and cathelicidin expression at 12 weeks correlated with treatment success. Low protease activity at baseline was a predictor of clinical response in the doxycycline treatment group.

Limitations: Healthy control subjects were not studied.

Conclusions: Improved clinical outcome correlated with reduced cathelicidin and protease activity, supporting both the mechanism of doxycycline and the potential of these molecules as biomarkers for rosacea. (J Am Acad Dermatol http://dx.doi.org/10.1016/j.jaad.2016.01.023.)

Key words: biomarker; cathelicidin; doxycycline; kallikrein; matrix metalloproteinase; papulopustular; rosacea; serine protease.

The origin of papulopustular rosacea is not yet fully understood, but multiple immune-mediated components are likely involved. Increased cutaneous cathelicidin levels, serine protease activity, and matrix metalloprotease (MMP) expression have been demonstrated to be involved in, and likely augment, the innate immune response in rosacea skin.[1,2]

Cathelicidins are antimicrobial peptides in human skin. Their direct antimicrobial action against a wide

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Investigator global assessment success rates for the intent-to-treat population were presented in poster form at the Society for Investigative Dermatology meeting on May 8-11, 2013 in Edinburgh, Scotland, the American Academy of Dermatology meeting on March 21-25, 2014 in Denver, CO, and the Winter Clinical meeting on January 17-22, 2014 in Waimea, HI. Investigator global assessment success rates for the subpopulation recently given a diagnosis of rosacea were presented in poster form at the Winter Clinical meeting on January 17-22, 2014 in Waimea, HI.

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range of bacteria serves as the basis for defense against infection; however, their activities also extend to host immunity and growth responses.[3] Human cathelicidin (hCAP18) is produced as an inactive precursor protein that is posttranscriptionally cleaved to produce the active cathelicidin peptide LL-37.[4]

Serine proteases in the skin, such as kallikrein (KLK)5 and KLK7, participate in the proteolytic activation of hCAP18 to LL-37.[5,6] Like hCAP18, KLKs are also released as inactive precursors that are subsequently activated by autocatalytic or proteolytic cleavage by other endopeptidases, such as MMPs.[7]

Recent observations indicate that abnormal production of LL-37 in the skin is implicated in a wide variety of inflammatory skin diseases, including psoriasis, atopic dermatitis, and rosacea.[1,8,9] Abnormal expression of KLK5 in rosacea skin causes aberrant activation of hCAP18 to LL-37.[1] Therefore, blocking activation of hCAP18 through inhibition of upstream endopeptidases may have therapeutic potential in relieving the inflammation of rosacea.

Doxycycline is known to be an effective treatment for rosacea.[10] Although the precise mechanism is still unknown, doxycycline is thought to exert its clinical effects by providing anti-inflammatory activity even at a subantimicrobial dosage.[11]

Doxycycline nonselectively inhibits MMPs by binding to the adjacent zinc and calcium atoms within their structural metal center, causing conformational changes and loss of enzymatic activity.[12] Doxycycline has also been shown to suppress activity of MMPs in a variety of human cells, including skin keratinocytes.[13-15] Through these actions, doxycycline indirectly suppressed KLK activity in keratinocytes in vitro, thereby suppressing the proteolytic activation of hCAP18 to LL-37.[16] It has been hypothesized that this action of doxycycline explains the anti-inflammatory activity in patients with rosacea.

This study aimed to verify that cathelicidin was increased in the skin of patients affected by rosacea in a large study population, that improvement in rosacea was related to normalization of cathelicidin levels, and that cathelicidin normalization can be achieved with doxycycline treatment.

CAPSULE SUMMARY

- Cathelicidin and skin proteases are known biomarkers in papulopustular rosacea. The mechanisms of doxycycline in treating rosacea are thought to be anti-inflammatory.
- This research verifies modified-release doxycycline reduces skin cathelicidin; biomarker levels in patients with rosacea correlate with therapeutic response.
- Biomarker diagnostics may be useful for predicting treatment outcomes in rosacea.

METHODS

Study design

This multicenter, randomized, double-blind, placebo-controlled, 12-week study was conducted in adults aged 18 to 70 years given a clinical diagnosis of papulopustular rosacea and having 5 to 40 papules or pustules present. Patients who used concomitant medications that might interfere with clinical assessments were excluded. The study was conducted at 12 investigational sites in accordance with federal and local regulatory requirements and was reviewed and approved by a central institutional review board (Compass Institutional Review Board LLC, Mesa, AZ) before study initiation.

Patients were randomly assigned to once-daily modified-release doxycycline capsules (30-mg immediate release/10-mg delayed release beads) (Oracea, Galderma Laboratories LP, Fort Worth, TX)[17] or placebo treatment in a 1:1 ratio. Efficacy and safety assessments and biomarker sample collections were conducted at baseline and weeks 2, 4, 8, and 12 unless otherwise noted. The primary efficacy end point was the change from baseline in inflammatory lesion counts at week 12. Secondary efficacy, biomarker, and safety end points are described below. Additional information can be found at clinicaltrials.gov (NCT01308619).

Clinical assessments

Efficacy end points included inflammatory lesion count and investigator global assessment (IGA) score. IGA score used a 5-point scale (0 = clear, 1 = near clear, 2 = mild, 3 = moderate, and 4 = severe). Clinical success on the IGA was defined as a score of 0 or 1.

Efficacy in subpopulations of patients with mild and newly diagnosed rosacea was further analyzed, including patients who had mild baseline scores, had fewer than 10 lesions at baseline, or had rosacea for less than 5 years. These subpopulations in the doxycycline treatment arm were compared with patients who had moderate baseline scores, had more than 15 lesions at baseline, or had rosacea for more than 20 years, respectively.

Laboratory assessments

Tape-strip samples for analysis of KLK, MMP, and total serine protease (pTP) activity and cathelicidin