Emerging therapies in rosacea

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Rosacea is a common skin disorder with multiple symptoms. The emergence of research that furthers understanding of pathophysiological mechanisms has created new targets for disease treatment. Specifically, there is a need for new treatments that address the various erythematous symptoms associated with rosacea. Systemic and topical therapies have both yielded positive results in treating rosacea with various medications. Subantimicrobial-dose doxycycline is one such promising treatment. Development of novel products in the near future should help achieve more satisfactory outcomes for patients. (J Am Acad Dermatol 2013;69:S57-65.)

Key words: carvedilol; ivermectin; medical therapy; permethrin; rosacea; subantimicrobial-dose doxycycline.

Rosacea represents a chronic inflammatory skin disorder with many clinical guises. These embrace transient and permanent erythema, inflammatory papules and pustules, phymatos changes, and ocular signs and symptoms. The pathophysiology is multifactorial and as yet not fully determined. However, the understanding of mechanisms involved in the cause of rosacea are emerging and recent molecular studies suggest that an altered innate immune response is involved in both the vascular and inflammatory disease seen in patients with rosacea. As appreciation of pathophysiology unfolds, there is opportunity to target the specific pathogenic factors and related clinical manifestations with novel agents. Numerous treatments, including topical metronidazole and azelaic acid and systemic tetracyclines, have been shown to be efficacious for the papules and pustules of rosacea. However, to date there have been few good treatment options for the facial redness commonly seen in rosacea attributable to inflammation and vascular change. Recent reports suggest novel therapies are on the horizon for treating the erythema of rosacea. The following outlines treatment developments and discusses the rationale for use and effect of low-dose tetracycline antibiotics, β-blockers, and antiparasitic agents for rosacea-related erythema. Novel adrenergic receptor agonists are considered elsewhere in this supplement.

SYSTEMIC THERAPIES
Subantimicrobial-dose tetracyclines
Appreciation of the inflammatory nature of rosacea and the growing concern about antibiotic-resistant bacteria emerging as a result of systemic antibiotics used in the management of a number of inflammatory skin conditions has prompted interest in the use of subantimicrobial doses of tetracycline antibiotics as a means of treating inflammation. There are currently 3 major tetracycline derivatives in clinical use: tetracycline, doxycycline, and minocycline. The antimicrobial activity of these agents is both dose and concentration dependent; each also has anti-inflammatory actions that are unrelated to antibiotic activity and occur at lower doses than those required to achieve a bactericidal affect (Fig 1). There is recognition that rosacea has pathogenic factors that result in inflammatory changes that are unrelated to bacteria but respond to antibiotic therapy. This has stimulated interest in exploiting the anti-inflammatory actions of the tetracyclines. In rosacea, subantimicrobial-dose doxycycline (SDD) is thought to act by multiple mechanisms (Table I). Cathelicidins are proinflammatory

Abbreviation used:
SDD: subantimicrobial dose doxycycline

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peptides linked to inflammation in rosacea. Most recently, doxycycline has been found to decrease the activity for the kallikrein 5 enzyme that is responsible for generating activated cathelicidins from procathelicidin. Doxycycline accomplishes this indirectly by inhibiting the matrix metalloproteinase enzymes responsible for generating activated kallikrein. This second-generation tetracycline is the first antibiotic to be studied at doses that are not bactericidal but have anti-inflammatory action in rosacea and other conditions; once-daily SDD (40 mg) has now been approved by regulatory bodies for treatment of rosacea. Microbial kinetics. SDD in dosage formulations of 20 mg twice a day and once-daily 40-mg delayed release have both been sufficiently studied to be granted non-antibiotic status by the US Food and Drug Administration. In addition to pharmacokinetic studies, long-term microbiologic studies have evaluated the impact of SDD on subgingival, intestinal, vaginal, and cutaneous flora. As have evaluated the impact of SDD on subgingival, intestinal, vaginal, and cutaneous flora. In addition to regulatory approval, SDD has both been sufficiently studied to be granted non-antibiotic status by the US Food and Drug Administration. In addition to regulatory approval, SDD has been applied for its antibiotic activity for the kallikrein 5 enzyme that is responsible for generating activated kallikrein. This second-generation tetracycline is the first antibiotic to be studied at doses that are not bactericidal but have anti-inflammatory action in rosacea and other conditions; once-daily SDD (40 mg) has now been approved by regulatory bodies for treatment of rosacea.

Clinical efficacy on inflammatory skin lesions in rosacea. Two phase III clinical trials evaluated the efficacy and safety of SDD for the treatment of moderate to severe rosacea. The studies, which included a total of 537 subjects, over a 16-week period, were randomized, double-blind, and placebo-controlled. Patients treated with SDD had significantly greater reduction of total inflammatory lesions at week 16 compared with patients who received placebo (P < .001). This trend was evident beginning at week 3, with a greater decrease in lesion count in the SDD group compared with the placebo group (P < .005), which continued through to week 16. Post hoc analysis showed that the efficacy was consistent regardless of the number of lesions at baseline and body weight; indeed, SDD was most effective in overweight patients with high numbers of lesions at baseline. A separate study comparing SDD with doxycycline (100 mg) in patients with moderate to severe papulopustular rosacea (N = 91). The results showed SDD achieved lesion reductions that were comparable with those seen with traditional-dose doxycycline (Fig 3). One point for consideration relates to the fact these studies did not consider different absorption coefficients in individuals, which might also have influenced efficacy.

Clinical efficacy of SDD on erythema in rosacea. Clinician erythema assessment has been considered as a secondary efficacy end point in some studies assessing SDD. In one such study the mean reduction from baseline in mean clinician erythema assessment score was significantly greater at week 16 in the actively treated subject arm than the placebo group (P = .017) whereas facial erythema decreased among subjects in a second randomized phase III trial evaluating anti-inflammatory doxycycline but the difference between the study groups did not reach significance.

Safety. Data from the phase III studies showed that SDD is generally safe and well tolerated. In these controlled studies, there were no cases of vaginal candidiasis or photosensitivity. Reports of gastrointestinal upset were also low. In the study comparing SDD with doxycycline (100 mg), the rate of gastrointestinal upset was 5 times higher with doxycycline (100 mg).

β-Blockers
Nonselective β-blockers decrease sympathetic activity and also have been reported to suppress flushing, which results in transient redness, particularly in patients with comorbid anxiety. β-Blockers are thought to act on flushing by blocking the β-adrenergic receptors on smooth muscles of cutaneous blood vessels, producing vasoconstriction. They may also reduce anxiety and tachycardia, which can exacerbate flushing reactions. Carvedilol, a newer nonselective β-blocker, has marked antioxidant and anti-inflammatory actions, which may contribute to an effect in rosacea.
There are only a few reports of β-blocker therapy in patients with rosacea. Craige and Cohen found that propranolol therapy (30-120 mg/d) was associated with fewer and less severe flushing episodes in 8 of 9 patients with rosacea. However, use of traditional β-blockers in normotensive individuals is limited by concerns of hypotension and bradycardia.

Hsu and Lee evaluated an alternative nonselective β-adrenergic receptor blocker, carvedilol, in refractory facial flushing and persistent erythema of rosacea with the implicit aims of achieving efficacy while reducing the likelihood of adverse events. In the first report by these researchers, carvedilol successfully treated rosacea-associated redness in a patient with severe refractory symptoms. The patient had both transient flushing and persistent erythema that had not responded to 4 weeks of treatment with a multitude of agents, including doxycycline, fexofenadine hydrochloride, dexamethasone, aspirin, topical corticosteroid, clonidine, and pimecrolimus cream. In this case report, carvedilol therapy (6.25 mg twice a day for 1 week followed by 6.25 mg 3 times a day) achieved a dramatic improvement in facial redness within 2 weeks. The patient monitored her blood pressure and pulse at home, and there were no observations of hypotension or bradycardia. The temperature of the skin on her cheek was reduced by 6.9°C and her assessment of severity based on a 10-point visual analog scale was reduced from a score of 10 to a score of 1. The patient was maintained on a regimen of carvedilol, doxycycline (100 mg every other day), and pimecrolimus 1% for 23 months.

In a second communication, Hsu and Lee reported good results with carvedilol therapy in 11 normotensive patients with rosacea unsuccessfully treated with numerous agents. The carvedilol dose was titrated from 3.25 mg 3 times a day to 25 mg/d and assessments included facial erythema, cheek temperature, patient assessment of severity, and adverse events. As shown in Fig 4,
significant clinical improvements occurred within 3 weeks of initiating therapy. In addition, the mean cheek temperatures were reduced by 2.2°C and the patients' assessments of severity improved (mean reduction of 6.3 on a 10-point visual analog scale). As the authors state, “low-dose carvedilol was effective in treating erythematotelangiectatic rosacea with rapid onset of symptom control.” Another encouraging finding was that other medications were discontinued or tapered. Based on these preliminary results, it seems that a larger scale controlled study would be beneficial.

**Oral ivermectin**

Single-dose oral ivermectin, a microfilaricide, has been used in immunocompromised patients with rosacea-like demodicidosis with good effect.

**TOPICAL THERAPIES**

Several topical therapies are being investigated for treatment of rosacea; all are primarily targeted
toward control of *Demodex folliculorum* and *D. brevis* mites. Agents recently studied include 5% permethrin, 10% crotamiton, and 1% ivermectin, all antiparasitic agents that have been used for treatment of a variety of infections.

The potential causative role of *Demodex* mites and associated commensals in the induction of rosacea has been under debate for many years. In human beings, 2 mite species (*D. brevis* and *D. folliculorum*) inhabit normal adult facial sebaceous follicles; they are not present in the newborn but sebaceous follicles are thought to become colonized during adolescence. Many researchers consider these mites to be a simple commensal on human skin. However, there is increasing evidence that these mites may be opportunistic pathogens with the potential to become parasitic if the host cutaneous environment facilitates or promotes their proliferation.

In many cases the *Demodex* will live symbiotically within human skin living off host sebum and acting as a commensal. In this context the host’s innate immune system remains tolerant to the presence of the *Demodex* mites. Hence, the presence of *Demodex* is not necessarily considered a pathogenic factor in the development of rosacea although *Demodex* proliferation has been considered as a primary causative factor for papulopustular rosacea by some authors and there are reports that demonstrate a higher density of *D. folliculorum* in patients with facial rosacea compared with control subjects. It has also been shown that proliferation of *D. folliculorum* results in an inflammatory response conforming to a rosacea-like demodicidosis or *Demodex* dermatitis. One study demonstrated a linear correlation between the presence of *D. folliculorum* and the levels of fibroblast-related matrix metalloproteinases-9 in patients with rosacea, supporting the fact that *D. folliculorum* proliferation in patients with papulopustular rosacea may represent an inflammatory cofactor. Use of topical agents with immunomodulatory effects including calcineurin antagonists have been reported to result in a rosacea-like dermatitis alongside an increase of *D. folliculorum* mites. Increased numbers of *D. folliculorum* mites in a patient with rosacea receiving an epidermal growth inhibitor (epidermal growth factor inhibitor) for cancer has also been reported. The authors hypothesized that the epidermal growth factor inhibitor was implicated in reducing the cutaneous defense mechanisms enabling the proliferation of *Demodex*. This concept around the particular physical barrier of the skin is of interest and it has been shown that patients with papulopustular rosacea have an increased facial pH and reduced skin surface hydration. These patients also have abnormal fatty acid composition of their skin surface lipid layer, with increased levels of myristic acid and linoleic acid and reduced levels of saturated fatty acids.
Several other reports have confirmed that immunosuppression associated with HIV and AIDS, chemotherapy for childhood leukemia, chronic dialysis, and use of phototherapy leads to an increase in the number of Demodex mites.

A recent meta-analysis has shown a significant association between Demodex species infestation and development of rosacea.

These reports also suggest that an increase in the critical mass of the mite can trigger inflammatory mechanisms that result in visible cutaneous inflammation. It is not clear whether the change in cutaneous microenvironment contributes to mite proliferation and/or the aberrant innate immune response allows for mite proliferation to the point where a humoral response is initiated and subsequent cutaneous inflammation ensues. However, previous studies and case reports would favor the latter as a contributing factor and one hypothesis poses that Demodex mites, like other cutaneous microbes, can take on different roles according to the host status.

Renewed interest in Demodex has arisen from recent work that has identified a D. folliculorum—associated bacterium (Bacillus oleronius) isolated from patients with papulopustular rosacea. It has been suggested that B. oleronius produces antigenic proteins that may play a role in papulopustular and ocular rosacea.

A further recent study has demonstrated that patients with erythematotelangiectatic rosacea show serum reactivity to 2 proteins from B. oleronius suggesting that this bacterium may play a role in the induction of erythematotelangiectatic rosacea. The proteins implicated were found to be similar to heat shock protein and an enzyme involved in regulating stress response of the bacterium.

**Permethrin**

There have been several case reports about use of topical permethrin in rosacea, usually in combination with or after oral ivermectin therapy. Aquilina et al found that oral ivermectin plus topical permethrin effectively resolved a rosacea-like facial Demodex infection in a patient with immune compromise. The patient had no response to either topical ketoconazole or metronidazole and had recent onset of rosacea-like papules and pustules associated with erythema, edema, and scales. Skin scraping and histologic examination of skin...
biopsy specimen showed a high concentration of Demodex. Because of the high numbers of mites and existing medications for comorbid conditions, an acaricidal regimen was prescribed. Within 2 weeks, there was a marked reduction in symptoms; topical permethrin cream was used to maintain results and no recurrence was reported after 1-year follow-up.

Allen et al\textsuperscript{22} reported successful treatment with oral ivermectin and topical permethrin in an immunocompetent patient with papulopustular rosacea that was refractory to other therapies. However, these researchers thought that Demodex infestation had a prominent role in the case, and noted they would make a diagnosis of rosacea-like demodicidosis. Notably, the patient had previously been treated unsuccessfully with topical permethrin alone, and skin scrapings and biopsy specimen showed significant follicular colonization with Demodex despite permethrin monotherapy.\textsuperscript{22} Similarly, Forstinger et al\textsuperscript{25} reported successful treatment of Demodex-associated rosacea symptoms in a man who had been refractory to conventional treatment (Fig 5). As in the other cases, this patient had numerous Demodex mites on skin scraping and histology, and a regimen of oral ivermectin followed by topical permethrin was prescribed.\textsuperscript{30} Marked symptomatic relief occurred within 2 weeks of the initial dose of oral ivermectin, and once-weekly topical permethrin was efficacious in maintaining results.\textsuperscript{25}

Crotamiton

Bikowski and Del Rosso\textsuperscript{33} performed a retrospective analysis of topical crotamiton treatment in patients with rosacea-like Demodex dermatitis. In 63 patients who had facial redness and rash, crotamiton 10% cream/lotion monotherapy twice daily resulted in a 50% or greater reduction in symptoms in 90.6% (56 of 62) (Fig 6). Noting that patients with recurrent, unchanged erythema, dryness/scaling, and roughness with or without papules and pustules had marked improvement even when diagnostic testing did not confirm presence of Demodex mites, the authors noted that “empirical treatment for Demodex dermatitis using crotamiton is beneficial for patients with these unresolved signs and symptoms.”\textsuperscript{33}

Although as noted above topical crotamiton 10% or permethrin 5% have been used to reduce the numbers of D folliculorum, they are frequently irritating and are therefore not tolerated well in all patients.

Ivermectin

Ivermectin is a strong acaricide with efficacy against Demodex in case reports.\textsuperscript{24,26} Topical formulations of ivermectin are being investigated in several conditions, including rosacea. In a recent controlled study of scabies, topical ivermectin 1% had efficacy that was more rapid than oral ivermectin and comparable with topical permethrin, and the authors
concluded that “topical ivermectin can be used as an alternative to permethrin.”

The significant impact on Demodex and possibly anti-inflammatory properties of topical ivermectin has prompted investigation into the development of a topical product. Controlled trials examining the impact of topical ivermectin in rosacea are underway and results should be available in the near future.

CONCLUSIONS

Rosacea continues to pose a significant clinical challenge; the clinical erythema associated with rosacea relates not only to the color associated with papules and pustules but also to the transient and persistent redness that frequently persists after effective treatment of the inflammatory lesions. There is currently an unmet need for new treatments, particularly those targeted toward resolving persistent erythema.

To date, there have been few effective treatments for erythema; patients are advised to avoid triggers involved in the innate immune response. However, although important, this does not achieve a satisfactory response in many cases. New treatments are on the horizon, and we look forward to seeing new products become available in the near future.

REFERENCES