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Commentary

**Additional evidence that rosacea pathogenesis may involve *demodex*: new information from the topical efficacy of ivermectin and praziquantel**

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**Abstract**

Additional evidence that *Demodex folliculorum* may contribute to the pathogenesis of papulopustular rosacea are new studies of two topical antiparasitic agents. Ivermectin and praziquantel have recently been shown to be effective in decreasing the severity of papulopustular rosacea. These two agents significantly differ in molecular structure, but yield similar antiparasitic mechanisms of action. Higher numbers of *Demodex* mites are found in the skin of patients with rosacea than in people with normal skin. If *Demodex* play a role in pathogenesis, then hypersensitivity to the mites, their flora, or their products could explain the observed efficacy of antidemodectic therapy.

**Keywords : parasite, papulopustular, treatment, mechanism.**

**Abbreviation: IVM (Ivermectin), AE (adverse event)**

**Introduction**

Several studies have shown that *Demodex folliculorum* mites, present on the facial skin of all humans, occur in much greater numbers on the faces of people with rosacea [1, 2, 3]. Rios-Yuil and Mercadillo-Perez found further evidence of more than twice the density *Demodex* mites in biopsies of the skin of patients with rosacea than in control patients with a variety of other conditions [1]. Moreover *D. folliculorum* was found in 80% of rosacea biopsies and in only 30% of control biopsies [1]. In affected skin of rosacea patients, 35% to 50% of them have increased *Demodex* load (>5 mites/cm<sup>2</sup>) [3].

Papulopustular rosacea is characterized by erythema, papules and pustules. Evidence appears to be mounting that an overabundance of *Demodex* or an abnormal response to *Demodex* may trigger an immune response in people with rosacea. Alternatively the bacterial flora associated with *Demodex* could help produce the inflammation seen in rosacea [1]. *Demodex* mites are most plentiful in the same regions of the face that are most commonly affected by rosacea - the cheeks, nose, chin, and forehead.

Recently published trials using two different topical anti-demodectic treatments: ivermectin and praziquantel, suggest that *Demodex* may be more central to the pathogenesis. These two agents share similar mechanisms of action and efficacy.

## **Ivermectin**

Ivermectin is a semi-synthetic macrocyclic lactone that shows broad-spectrum anti-parasitic activity. It has been successfully used to treat parasitic infections, including onchocerciasis, strongyloidiasis, and many other conditions such as pediculosis and scabies. As an antiparasitic agent, it binds with high affinity to glutamate-gated chloride channels, which occur in invertebrate nerve and muscle cells, causing an increase in the permeability of the cell membrane to chloride ions with hyperpolarization of the nerve or muscle cell. Hyperpolarization results in paralysis and death of the parasite either directly or by causing the worms to starve [4, 15].

Topically applied ivermectin has recently been reported to have efficacy in papulopustular rosacea. Ivermectin shows broad-spectrum anti-parasitic activity and kills the *Demodex* mites that reside in the pilosebaceous units [5, 15]. Ivermectin also has anti-inflammatory effects; it decreases cellular and humoral immune responses [5, 15].

Recent clinical studies of ivermectin on papulopustular rosacea show that it was superior to vehicle in reducing inflammatory lesion counts and clearance of rosacea, and tolerability was excellent. Two identically designed, randomized, double-blind, 16 week, vehicle-controlled studies of ivermectin 1% cream were conducted in subjects with moderate to severe papulopustular rosacea. Investigators evaluated their progress at weeks 6, 9, 12, and 16. In both studies (n=478 and n=484), ivermectin was superior to vehicle in reducing inflammatory lesion counts (76.0% and 75.0% for ivermectin compared with 50.0% for both vehicle groups) [9, 15]. For the Investigators Global Assessment, investigators judged subjects to be clear or almost clear in 38% and 40% with ivermectin compared with 12% and 19% for vehicle (both P<.001). Tolerability was excellent with less than 1% of subjects reporting cutaneous adverse events [9, 15].

In a second phase of the above vehicle-controlled study, a 9-month, investigator-blinded treatment period in which patients who had previously used the vehicle instead used azelaic acid 15% gel twice daily whereas those using topical ivermectin continued [9,15 ]. The treatment-related dermatologic adverse event rate was lower in the ivermectin-treated subjects compared with the azelaic acid-treated subjects (1.3% versus 5.3%, respectively) [9, 15]. Comparisons of efficacy cannot be directly made since there were two different treatment periods.

In an additional 16 week randomized controlled trial, ivermectin 1% cream was compared with metronidazole 0.75% cream [10, 15]. A total of 962 subjects were randomized to receive IVM 1% (n=478) or metronidazole 0.75% (n=484). At week 16, IVM 1% was significantly superior to metronidazole 0.75% in terms of reduction from baseline in inflammatory lesions (83.0% vs. 73.7%; p<0.001). Incidence of AEs was comparable between groups and local tolerability was better for IVM 1% [10, 15].

## **Praziquantel**

Praziquantel is a synthetic trioxolane used as a treatment for all varieties of schistosomiasis as well as infections with human and animal cestodes and trematodes. Praziquantel works by causing severe spasms and paralysis of the worm muscles. This paralysis is likely caused by a rapid calcium influx inside the parasite [11]. This agent may have anti-inflammatory activity in as much as it has the capacity to decrease chitinase 3-like 1 protein (YKL-40) levels when parasite infected people are treated. This protein is produced by inflammatory cells and is elevated in some inflammatory conditions [12].

Recently, praziquantel ointment was tested in subjects with papulopustular rosacea [13]. Subjects with rosacea (n = 65) participated in a 16-week, randomized, single-blind pilot study of the effects of twice-daily monotherapy with 3% praziquantel ointment compared with vehicle. Efficacy was assessed clinically using the Investigator's Global Assessment Scale (IGAS) and the Clinical Erythema Assessment Scale (CEAS).

Scores on the IGAS and CEAS showed praziquantel ointment to have a significant therapeutic advantage over the vehicle treatment. At week 16, the praziquantel group demonstrated a statistically significant greater reduction in CEAS score than the placebo group (P < 0.001). Analysis of CEAS scores showed that 41.9% of patients in the praziquantel group and 18.2% of those in the vehicle group achieved a CEAS score equivalent to a rating of "none". The praziquantel -treated group also experienced a statistically significant improvement in comparison with the vehicle group at week 16 (P < 0.001). No serious treatment-related adverse events occurred in either treatment group [13].

## **Perioral Dermatitis and Rosacea**

Erythematous papules in a perioral distribution represent a distinct clinical entity, perioral dermatitis. Some have hypothesized that perioral dermatitis and papulopustular rosacea are related conditions inasmuch as they clinically, histologically, and behaviorally respond to the same therapies.

Investigators recently reported the results of a randomized pilot study using topical praziquantel ointment 3% as an effective treatment for perioral dermatitis. This was a single-center, randomized, single-blind, vehicle-controlled pilot study in adult patients (n = 46) with 4 weeks of treatment and 4 weeks of follow-up. Praziquantel was superior to vehicle using measures including the Investigator's Global Assessment (IGA) score and the Perioral Dermatitis Severity Index (PODSI). No serious treatment-related adverse events occurred in either group [14].

## Rosacea Pathophysiology and Demodex

The pathophysiology of rosacea is very complex. Figure 1 displays the possible pathophysiologic relationships between *Demodex* and rosacea-related inflammation. Toll-Like Receptor 2 (TLR-2), involved in recognition of foreign substances and activating the immune system, is upregulated in rosacea. Dust mites antigens can activate TLR-2, and *Demodex* may be able to activate TLR-2 as well as many downstream proinflammatory components including kallekrein, cathelicidins, and alarmins. These activations can lead to inflammatory cell recruitment and inflammation. Similarly, *Demodex* may be able to directly activate inflammasomes, which upregulate interleukin 1- $\beta$ , which can in turn activate tumor necrosis factor- $\alpha$  and interleukin-8. Both of these can similarly lead to inflammatory cell recruitment and inflammation.

Ivermectin and praziquantel both have antiparasitic activity, which likely affect *Demodex*. In addition, ivermectin has reported antimicrobial and antiinflammatory activities. It decreases cellular and humoral immune responses, reduces neutrophil phagocytosis, chemotaxis, and oxidant production by phagocytes, and significantly regulates TNF- $\alpha$ , IL-1 $\beta$ , and IL-10.

## Summary

There are now a number of studies that link *Demodex* to rosacea. Furthermore, other studies have demonstrated the efficacy and tolerability of both antiparasitic agents -- ivermectin and praziquantel as topical treatment for rosacea. Topical praziquantel appears to be efficacious in a rosacea-related condition, perioral dermatitis. Although ivermectin and praziquantel clearly have antiparasitic activity, which could explain their respective roles in improving rosacea, both have demonstrated putative anti-inflammatory activity. *Demodex* may indeed play a role in rosacea pathogenesis, but more work needs to be done to help understand the pathophysiology of this enigmatic condition.

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Figure 1 displays the possible pathophysiologic relationships between Demodex and rosacea-related inflammation. Toll-Like Receptor 2 (TLR-2) is upregulated in rosacea. Demodex may be able to activate TLR2 as well as many downstream proinflammatory components including kallekrein, cathelicidins, and alarmins, These activations can lead to inflammatory cell recruitment (macrophages and neutrophils ) which up regulate COX2, IL-8, and TNF, lead to inflammation and pain. Similarly, Demodex may be able to directly activate inflammasomes, which upregulate interleukin 1- $\beta$ , which in turn activate tumor necrosis factor- $\alpha$ , COX2, and interleukin-8. All of these can similarly lead to inflammatory cell recruitment and inflammation. Ivermectin and praziquantel both have antiparasitic activity which likely affect Demodex. In addition, ivermectin decreases cellular and humoral immune responses, reduce neutrophil phagocytosis, chemotaxis and oxidant production by phagocytes, and significantly regulate TNF- $\alpha$ , IL-1 $\beta$  and IL-8.