doi:10.36849/JDD.6932

Topical Ivermectin is Associated With Improved Erythematotelangiectatic, Papulopustular, and Phymatous Rosacea in a Secondary Analysis

Rohan Singh BS,[a] Patrick O. Perche BS,[a] Katherine A. Kelly BS,[a] Madison K. Cook BS,[a] Esther A. Balogh MD,[a] Irma M. Richardson MHA,[a] Steven R. Feldman MD PhD[a,b,c]

[a]Center for Dermatology Research, Department of Dermatology, Wake Forest School of Medicine, Winston-Salem, NC
[b]Department of Pathology, Wake Forest School of Medicine, Winston-Salem, NC
[c]Department of Social Sciences & Health Policy, Wake Forest School of Medicine, Winston-Salem, NC

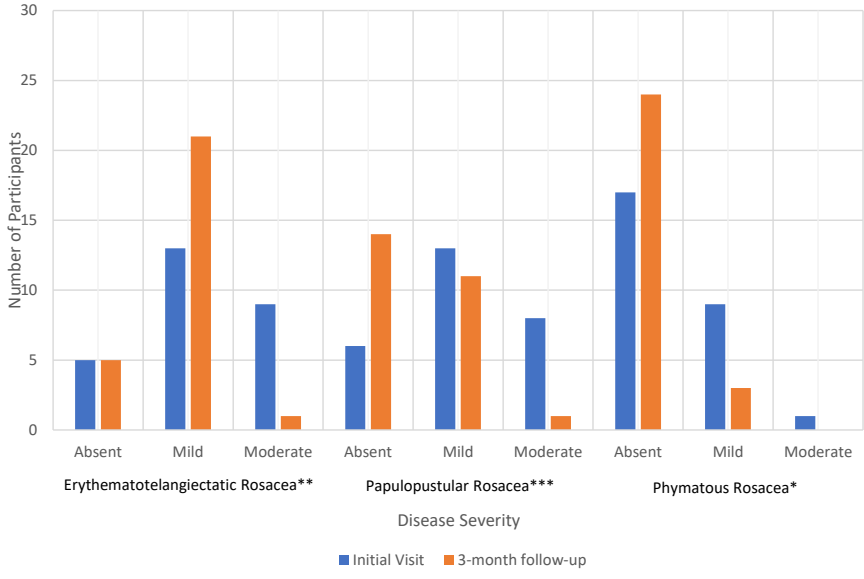
INTRODUCTION

Rosacea has variable clinical presentation consisting of four overlapping phenotypes: erythematotelangiectatic, papulopustular, phymatous, and ocular.[1] Rosacea's pathogenesis involves increased cutaneous density of *Demodex folliculorum* mites, which drive inflammation through activation of Toll-like receptor-2.[1,2] Thus, topical ivermectin (IVM) 1.0% cream's anti-inflammatory and acaricidal activity provides an effective and targeted treatment for moderate-to-severe rosacea. However, literature assessing IVM is limited to efficacy in treating the papulopustular presentation, limiting generalizability.[1,3,4] Although our primary endpoint was to assess patient adherence, the objective of this secondary analysis was to assess IVM efficacy in rosacea, regardless of clinical presentation.

METHODS

Thirty (30) adult subjects at Atrium Health Wake Forest Baptist Dermatology clinics were recruited after IRB approval. Inclusion criteria were age ≥18 years, working knowledge of English, and clinical rosacea diagnosis (ICD-10: L71.9). Exclusion criteria were diagnosis of skin condition other than rosacea and known IVM allergy. All used IVM cream 1% once daily for three months. Subjects were followed at two visits: baseline and three-month follow-up to approximate real-world use. Adherence was assessed using the Medication Events Monitoring System® cap. Disease severity was assessed using the Investigators Global Assessment (IGA) and Rosacea Severity Indices Global Assessment of Subtypes. One team member assessed the severity at each visit. Subjects also self-reported severity using a patient self-assessment tool (PSA), based on IGA. Three subjects

FIGURE 1. Rosacea severity over treatment.



Rosacea severity by presentation per the Rosacea Severity Indices Global Assessment by Subtypes.
*P=0.054, **P<0.05, ***P<0.01. Statistical significance determined using *Fisher's Exact Test*.

were excluded from the analysis (n=1 due to failure to follow protocol, and n=2 were lost to follow-up). Data were analyzed for differences by mean score with *Student's t-test* and percent of respondents with *Fisher's Exact Test* using SAS Software 9.4.

RESULTS

Subjects were mean age 62 (range 29-85), 70% female, and 93% Caucasian. Mean adherence was 62% over treatment period. At baseline, mean IGA and PSA were both 2.4. A total of 19/27 subjects had >1 rosacea clinical presentation. At three-month follow-up, mean IGA was 1.4 and PSA 1.5 (P<0.0001 and P<0.001, respectively). Severity of erythematotelangiectatic, papulopustular, and phymatous presentations improved from baseline (9 moderate, 13 mild, and 5 absent to 1 moderate, 21 mild, and 5 absent, P<0.05; 8 moderate, 13 mild, and 6 absent to 1 moderate, 11 mild, and 14 absent, P<0.01; and 1 moderate, 9 mild, and 17 absent to 0 moderate, 3 mild, and 24 absent; P=0.054, respectively) (Figure 1). Adverse events were reported (n=4 subjects) and included burning or stinging (n=3), scarring, dryness, itching, and swelling (n=1 for all).

DISCUSSION

In our cohort, despite incomplete adherence, IVM improved the severity of erythematotelangiectatic, papulopustular, and phymatous rosacea presentations. Our study was powered to assess large differences in adherence and provided only a limited cohort and no control group for assessing efficacy across rosacea types in this secondary analysis. The *Demodex folliculorum* mite is involved in the pathogenesis of rosacea, not limited to papulopustular type.[2,5] Thus, IVM may target rosacea's pathogenesis, regardless of presentation.[2,5] While current literature largely evaluates efficacy of IVM in the papulopustular presentation, results from our cohort suggest IVM may be efficacious in the treatment of the erythematotelangiectatic and phymatous presentations. Our findings support the possibility IVM may have efficacy for all rosacea presentations.

DISCLOSURES

Feldman has received research, speaking, and/or consulting support from a variety of companies including Galderma, GSK/Stiefel, Almirall, Leo Pharma, Baxter, Boeringer Ingelheim, Mylan, Celgene, Pfizer, Valeant, Taro, Abbvie, Cosmederm, Anacor, Astellas, Janssen, Lilly, Merck, Merz, Novartis, Regeneron, Sanofi, Novan, Parion, Qurient, National Biological Corporation, Caremark, Advance Medical, Sun Pharma, Suncare Research, Informa, UpToDate, and National Psoriasis Foundation. He is the founder and majority owner of www.DrScore.com and founder and part owner of Causa Research, a company dedicated to enhancing patients' adherence to treatment. Singh, Perche, Kelly, Cook, Balogh, and Richardson have no conflicts of interest to disclose.

IRB approval status: Reviewed and approved by Wake Forest University Health Sciences; approval IRB00062694

Funding sources: Funded by Galderma.

REFERENCES

1. Ebbelaar CCF, Venema AW, Van Dijk MR. Topical ivermectin in the treatment of papulopustular rosacea: a systematic review of evidence and clinical guideline recommendations. *Dermatol Ther (Heidelb).* 2018;8(3):379-387. doi: 10.1007/s13555-018-0249-y.
2. Schaller M, Gonser L, Belge K, et al. Dual anti-inflammatory and anti-parasitic action of topical iv*ermectin 1% in papulopustular rosacea.* J Eur Acad Dermatol Venereol. 2017;31(11):1907-1911. doi: 10.1111/jdv.14437.
3. Schaller M, Kemény L, Havlickova B, et al. A randomized phase 3b/4 study to evaluate concomitant use of topical ivermectin 1% cream and doxycycline 40-mg modified-release capsules, versus topical ivermectin 1% cream and placebo in the treatment of severe rosacea. *J Am Acad Dermatol.* 2020;82(2):336-343. doi: 10.1016/j.jaad.2019.05.063.
4. Husein-El, Ahmed H, Steinhoff M. Efficacy of topical ivermectin and impact on quality of life in patients with papulopustular rosacea: A systematic review and meta-analysis. *Dermatol Ther.* 2020;33(1):e13203. doi: 10.1111/dth.13203.
5. Chang YS, Huang YC. Role of Demodex mite infestation in rosacea: A systematic review and meta-analysis. *J Am Acad Dermatol.* 2017;77(3):441-447.e6. doi: 10.1016/j.jaad.2017.03.040.

AUTHOR CORRESPONDENCE

Rohan Singh BS
E-mail:..... rs.rohansingh@outlook.com