Topical Ivermectin for the Treatment of Papulopustular Rosacea: A Review

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Abstract

Rosacea is a common inflammatory skin disorder that affects many Americans. Currently, oral and topical antimicrobials are among the most effective medications used. Ivermectin 1% cream was recently approved for the treatment of papulopustular rosacea. The primary objective of this article is to provide a clinical review of the efficacy and safety of ivermectin 1% cream.

Introduction

Rosacea is estimated to affect nearly 16 million Americans.[1] Patients with lighter skin types are most often affected by rosacea. However, those of darker skin types are not entirely exempt from this diverse disorder.[2] Rosacea is defined as an inflammatory skin disorder characterized by the presence of inflammatory papules and pustules, erythema, and telangiectases distributed in the central facial region.[3,4] Phymatous and ocular manifestations are also characteristic findings seen in rosacea.[3,4]

The National Rosacea Society Expert Committee classifies rosacea into four distinct subtypes.[2,5] However, patients do not always conform to one specific subtype, and there may be significant overlap between groups. Erythematotelangiectatic rosacea (ETR) is characterized by flushing and erythema of the central facial region with or without telangiectases.[5] Papulopustular rosacea (PPR) is characterized by persistent central facial erythema with transient inflammatory papules and pustules.[5] Phymatous rosacea (PhR) is characterized by thickened, nodular skin and rhinophyma.[5] Finally, ocular rosacea (OR) is characterized by the presence of ocular dryness, conjunctivitis, and blepharitis in addition to burning and stinging sensations in the eye.[5]

Rosacea is hypothesized to be the result of vascular dysregulation and abnormal inflammatory responses ultimately resulting in chronic vasodilation and inflammation.[6] Additionally, a variety of triggers including stress, heat, hot liquids, spicy foods, and alcohol exacerbate the underlying vasodilation and inflammation and are associated with flares of rosacea.[4] Innate immune mechanisms like antimicrobial peptides, serine proteases, and toll-like receptors (TLRs) have been implicated in the inflammatory and vasodilatory processes responsible for rosacea.[7] Specifically, elevated levels of cathelicidins (i.e. LL-37) and kallikrein 5 (KLK5) have been found in the skin of patients with rosacea.[8-10] Additionally, patients with rosacea have been found to have an increased density of *Demodex* mites, specifically *D. folliculorum* and *D. brevis*, associated with their pilosebaceous units, and antigenic proteins from *Bacillus oleronius* isolated from *Demodex* mites may play a role in the underlying pathophysiology of rosacea.[11] As such, rosacea may be the result of an abnormal innate immune response to environmental and/or infectious stimuli.

Oral and topical antimicrobials have been used successfully for the treatment of rosacea, and ivermectin 1% cream was recently approved for the treatment of papulopustular rosacea. The primary objectives of this article are to review the current literature surrounding the use of topical ivermectin in the treatment of rosacea and to provide further insight with regard to administration and adverse effects.

Mechanism of Action

Ivermectin is an avermectin antiparasitic agent that is used orally for the treatment of strongyloidiasis, demodicidosis, pediculosis, and scabies, in addition to other parasitic/helminthic infections. It exerts its effect by binding to parasite glutamate-gated ion channels, resulting in increased permeability to chloride ions.[12,13] Hyperpolarization of the cell ensues, ultimately resulting in the death of the parasite. Additionally, ivermectin has been shown to display anti-inflammatory properties through inhibition of lipopolysaccharide-induced inflammation. Specifically, a reduction in TNF-alpha and interleukin-1b (IL-1b) have been documented along with a corresponding increase in interleukin-10 (IL-10), an anti-inflammatory cytokine.[14]

Clinical Trials

The Ivermectin Phase III Study Group reported the results of two, 12-week, randomized, double-blind, parallel-group, vehicle-controlled studies in 2014. The primary objective of each study was to determine efficacy based on the improvement in Investigator's Global Assessment (IGA) of severity scores and the reduction in inflammatory lesion count.[15] Approximately 700 patients were enrolled in each study, and patients were allocated to receive either ivermectin 1% cream or vehicle in a 2:1 ratio.[15] Patients were then instructed to apply either ivermectin 1% cream or vehicle once daily. The patient population was primarily Caucasian (96.2% and 95.3%) and female (68.2% and 68.7%) with an mean age of approximately 50 years old (50.4 +/- 12.09 and 50.2 +/- 12.29).[15] Mean inflammatory lesion counts upon initiation of the trial were 31 and 33 (SD +/- 14.33, 13.7), and the majority of patients had moderate rosacea as defined by an IGA score of 3 (82% and 72.9%).[15]

Following 12 weeks of therapy, the percentage of patients able to achieve an IGA grade of clear or almost clear in the ivermectin groups were 38.4% and 40.1%, compared to 11.6% and 18.8% in the vehicle groups ($p<0.001$).[15] Additionally, a significant difference in IGA scores was appreciated as early as four weeks in each study.[15] The mean reduction in inflammatory-lesion counts were 75% and 76% with a mean difference of -8.16 [-10.12, -6.13] and -8.22 [-10.18, -6.25] in comparison to vehicle for each of the ivermectin groups ($p<0.001$).[15] In comparison, a 50% reduction in inflammatory-lesion counts was observed in the vehicle groups from both trials ($p<0.001$).[15] Additionally, quality-of-life assessments, as measured by Dermatology Life Quality Index (DLQI) and RosaQoL, were significantly improved in the ivermectin group in comparison to vehicle.[15]

Both trials were then extended for an additional 40 weeks in order to assess long-term safety. Patients initially allocated to receive ivermectin 1% cream were continued on a once-daily topical-application regimen. Patients in the vehicle group were then assigned to receive azelaic acid 15% gel applied topically twice daily. A total of 622 and 636 patients continued the trial into its extension phase, and approximately 80% of the patients completed the study.[16] Dermatologic adverse effects were noted in 7.8% and 9.8% of the patients in the ivermectin groups in comparison to 12.9% and 16.3% in the vehicle/azelaic-acid groups.[16] Notably, no serious or severe adverse events were related to either study medication.[16] While it was not the primary objective of the extension phases of the trials, efficacy at 52 weeks was addressed. A total of 71.1% and 76% of patients in the ivermectin groups were able to achieve IGA grades of clear or almost clear.[16]

Another 16 week, randomized, investigator-blinded, parallel-group study was conducted on behalf of the Ivermectin Phase III study group in Europe. The study compared once-daily application of ivermectin 1% cream with twice-daily application of metronidazole 0.75% cream. The primary objective of this study was to determine whether ivermectin 1% cream was superior to metronidazole 0.75% cream with regard to reductions in inflammatory-lesion

counts in patients with papulopustular rosacea.[17] A total of 962 patients with moderate to severe papulopustular rosacea and inflammatory-lesion counts between 15 and 70 were randomized in a 1:1 ratio to receive either ivermectin 1% cream or metronidazole 0.75% cream.[17] The mean number of inflammatory lesions at baseline was 32.46 +/- 13.36, and 83.3% of patients had moderate rosacea based on IGA scores.[17] The percent reduction in inflammatory-lesion counts in the ivermectin group was 83% in comparison to 73.7% in the metronidazole group, with an absolute difference of 9.3% ($p<0.001$).[17] Additionally, 84.9% of patients in the ivermectin group were able to achieve IGA grade clear or almost clear in comparison to 75.4% in the metronidazole group ($p<0.001$).[17] Similar findings were observed in each group with regard to patient-reported outcomes.[17]

Adverse Effects

The most commonly reported adverse effects associated with ivermectin 1% cream were burning sensations, dry skin, skin irritation, pruritus, skin pain, and eye pain.[15-17]

Administration

Ivermectin 1% cream should be applied topically once daily to the affected areas of the face, typically the forehead, nose, chin, and cheeks.[13] A pea-sized amount should be used and spread as a thin layer, avoiding the eyes and mouth.[13]

Discussion

Ivermectin 1% cream is a novel antimicrobial agent for the topical treatment of papulopustular rosacea. Its efficacy and safety are well documented in the aforementioned clinical trials. Additionally, it has favorable patient-reported outcomes and a minimal side-effect profile.

Metronidazole, azelaic acid, and doxycycline are the most effective medications available for the treatment of papulopustular rosacea.[18] Their anti-inflammatory effects are the proposed mechanism of action in papulopustular rosacea.[10,19] Likewise, ivermectin has been shown to possess anti-inflammatory properties, in addition to effectiveness against demodicidosis. This dual-action property might explain its effectiveness in the treatment of papulopustular rosacea. However, the exact role that *Demodex* mites play in the underlying pathogenesis of rosacea has yet to be fully elucidated.

Conclusion

There is documented evidence that ivermectin 1% cream is superior to metronidazole 1% cream with regard to percent reduction in inflammatory-lesion counts. However, it is difficult to conclude that this is a clinically significant difference. Additionally, it is difficult to determine whether this difference is applicable to metronidazole gel as well. Likewise, ivermectin 1% cream is likely better tolerated than azelaic acid. However, it is not possible to say that it is superior with regard to efficacy, as this was not the primary objective of the trial.

As with all new medications that come to market, cost will likely be the largest barrier to its use. However, ivermectin 1% cream should be considered in patients who fail or are unable to tolerate more affordable modalities.

References

1. National Rosacea Society. Rosacea Riddle Now Threatens More Than 16 Million Americans [Internet]. Chicago: National Rosacea Society; 2010 Apr 1 [cited 2015 Mar 22]; [about 2 screens]. Available from: http://www.rosacea.org/press/archive/20100401.php.

2. Powell F, Raghallaigh S, eds. Rosacea and Related Disorders. In: Bolognia J, Jorizzo J, Schaffer J, eds. Dermatology, vol. 1. Philadelphia: WB Sauders; c2012. 561 p.

3. Tan J, Berg M. Rosacea: Current State of Epidemiology. J Am Acad Dermatol. 2013;69:S27-35.

4. Del Rosso JQ. Management of Cutaneous Rosacea: Emphasis on New Medical Therapies. Expert Opin Pharmacother. 2014;15(14):2029-2038.

5. Wilkin J, Dahl M, Detmar M, et al. Standard Classification of Rosacea: Report of the National Rosacea Society Expert Committee on the Classification and Staging of Rosacea. J Am Acad Dermatol. 2002;46(4):584-587.

6. Feldman S, Huang W, Huynh T. Current Drug Therapies for Rosacea: A Chronic Vascular and Inflammatory Skin Disease. J Manag Care Pharm. 2014;20(6):623-629.

7. Cribier B. Pathophysiology of Rosacea: Redness, Telangiectasia, and Rosacea. Ann Dermatol Venereol. 2011;138(S3):S184-91.

8. Yamasaki K, DiNardo A, Bardan A, et al. Increased Serine Protease Activity and Cathelicidin Promotes Skin Inflammation in Rosacea. Nat Med. 2007;13(8):975-980.

9. Del Rosso JQ, Gallo R, Kircik L, et al. Why is Rosacea Considered to be an Inflammatory Disorder? The Primary Role, Clinical Relevance, and Therapeutic Correlations of Abnormal Innate Immune Response in Rosacea-Prone Skin. J Drugs Dermatol. 2012;11:694-700.

10. Del Rosso JQ, Thiboutot D, Gallo R, et al. Consensus Recommendations from the American Acne and Rosacea Society on the Management of Rosacea, Part 3: A Status Report on Systemic Therapies. Cutis. 2014;93:18-28.

11. O'Reilly N, Menezes N, Kavangh K. Positive Correlation Between Serum Immunoreactivity to Demodex-associated Bacillus Proteins and Erythematotelangiectatic Rosacea. Br J Dermatol. 2012;167(5):1032-1036.

12. Wolstenholme A, Rogers A. Glutamate-gated Chloride Channels and the Mode of Action of the Avermectin/Milbemycin Anthelminthics. Parasitology. 2005;131:S85-95.

13. Soolantra (Ivermectin) Topical Cream, 1% [Prescribing Information]. Fort Worth, TX: Galderma Laboratories, L.P. 2014.

14. Ci X, Li H, Yu Q, et al. Avermectin Exerts Anti-inflammatory Effect by Down regulating the Nuclear Factor Kappa-B and Mitogen-activated Protein Kinase Activation Pathway. Fundam Clin Pharmacol. 2009;23(4):449-455.

15. Stein Gold L, Kircik L, Fowler J, et al. Efficacy and Safety of Ivermectin 1% Cream in the Treatment of Papulopustular Rosacea: Results of Two Randomized, Double-Blind, Vehicle-Controlled Pivotal Trials. J Drugs Dermatol. 2014;13(3):316-323.

16. Stein Gold L, Kircik L, Fowler J, et al. Long-Term Safety of Ivermectin 1% Cream vs Azelaic Acid 15% Gel in Treating Inflammatory Lesions of Rosacea: Results of Two 40-Week Controlled, Investigator-Blinded Trials. J Drugs Dermatol. 2014;13(11):1380-1386.

17. Taieb A, Ortonne J, Ruzicka T, et al. Superiority of Ivermectin 1% Cream over Metronidazole 0.75% Cream in Treating Inflammatory Lesions of Rosacea: A Randomized, Investigator-Blinded Trial. Br J Dermatol. 2014. [Epub Ahead of Print].

18. Van Zuuren E, Kramer S, Carter B, et al. Effective and Evidence-Based Management Strategies for Rosacea: Summary of a Cochrane Systematic Review. Br J Dermatol. 2011;165:760-781.

19. Del Rosso JQ, Thiboutot D, Gallo R, et al. Consensus Recommendations from the American Acne and Rosacea Society on the Management of Rosacea, Part 2: A Status Report on Topical Agents. Cutis. 2013;92:277-284.

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