

Treatment of Rosacea With Concomitant Use of Topical Ivermectin 1% Cream and Brimonidine 0.33% Gel: A Randomized, Vehicle-controlled Study

Linda Stein Gold MD,^a Kim Papp MD PhD FRCPC,^b Charles Lynde MD FRCPC,^c Edward Lain MD MBA,^d Melinda Gooderham MSc MD FRCPC,^e Sandra Johnson MD FAAD,^f and Nabil Kerrouche MSc^g

^aDepartment of Dermatology, Henry Ford Medical Center, Detroit, MI, USA ^bK Papp Clinical Research and Probitry Medical Research, Waterloo, ON, Canada ^cLynde Institute for Dermatology and Probitry Medical Research, Markham, ON, Canada ^dAustin Institute for Clinical Research, Pflugerville, TX, USA ^eQueen's University, Kingston, ON, SKiN Centre for Dermatology and Probitry Medical Research, Peterborough, ON, Canada ^fJohnson Dermatology, Fort Smith, AR, USA ^gGalderma R&D Sophia Antipolis, Biot, France

ABSTRACT

BACKGROUND: There is currently a lack of data on the simultaneous treatment of different features of rosacea. Individually, ivermectin 1% (IVM) cream and brimonidine 0.33% (BR) gel have demonstrated efficacy on inflammatory lesions and persistent erythema, respectively. **OBJECTIVE:** To evaluate the efficacy, safety, patient satisfaction, and optimal timing of administration of IVM associated with BR (IVM+BR) versus their vehicles in rosacea (investigator global assessment [IGA] ≥ 3). **METHODS:** Multicenter, randomized, double-blind study including subjects with rosacea characterized by moderate to severe persistent erythema and inflammatory lesions. The active treatment group included the IVM+BR/12 weeks subgroup (once-daily BR and once-daily IVM for 12 weeks), and the IVM+BR/8 weeks subgroup (once-daily BR vehicle for 4 weeks followed by once-daily BR for the remaining 8 weeks and once-daily IVM for 12 weeks). The vehicle group received once-daily BR vehicle and once-daily IVM vehicle for 12 weeks. **RESULTS:** The association showed superior efficacy (IGA success [clear/almost clear]) for erythema and inflammatory lesions in the total active group (combined active subgroups) compared to vehicle (55.8% vs. 36.8%, $P=0.007$) at week 12. The success rate increased from 32.7% to 61.2% at hour 0 and hour 3, respectively, in the IVM+BR/12 weeks subgroup, and from 28.3% to 50% in the IVM+BR/8 weeks subgroup. Reductions in erythema and inflammatory lesion counts confirmed the additive effect of BR to IVM treatment. Subjects reported greater improvement in the active subgroups than in the vehicle group, and similar rates for facial appearance satisfaction after the first 4 weeks of treatment in both active subgroups. All groups showed similar tolerability profiles. **CONCLUSION:** Concomitant administration of IVM cream with BR gel demonstrated good efficacy and safety, endorsing the comprehensive approach to this complex disease. Early introduction of BR, along with a complete daily skin care regimen may accelerate treatment success without impairing tolerability.

J Drugs Dermatol. 2017;16(9):909-916.

INTRODUCTION

Rosacea is a chronic skin disease with prevalence varying from < 1% to > 20%, and it is most commonly reported in people with fair skin.¹⁻⁵ Recent studies have re-estimated the prevalence at approximately 5%-10% of the general population.⁶ The central facial skin is the predominant site of involvement. Thus, patients report negative impact of rosacea on their self-esteem and social/professional interactions.⁷⁻⁹ The etiology of rosacea remains unknown, with both genetic and environmental factors, as well as microorganisms such as *Demodex folliculorum*, potentially contributing to the pathogenesis.¹⁰⁻¹⁴ Rosacea is typically characterized by persistent facial erythema and recurrent eruptions of inflammatory lesions (papules/pustules). The previous approach to the diagnosis and classification of rosacea was based on disease subtypes. However, this approach did not address the entire spectrum of clinical presentation, leading to suboptimal disease management.¹⁵⁻¹⁷ The ROSacea COnsensus (ROSCO) panel of experts recently shifted the focus for the diagnosis and classification of rosacea

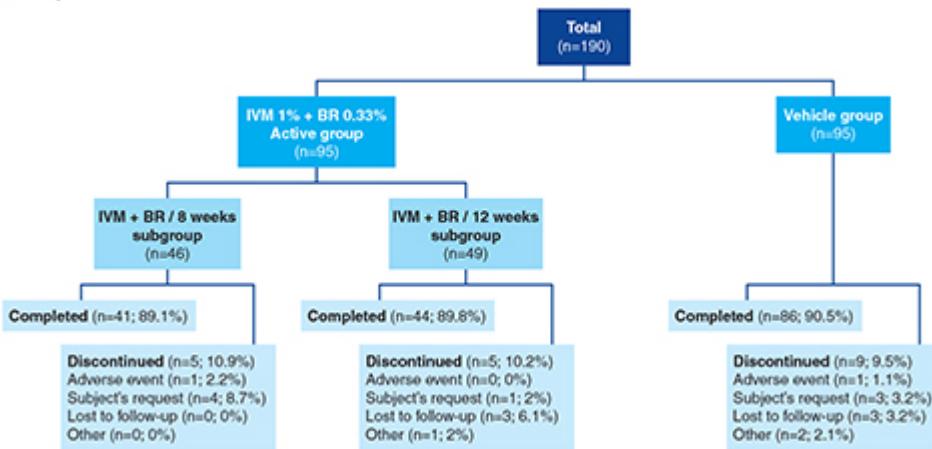
to a phenotype-led approach, allowing clinicians to better customize disease management.^{15,16, 18} Currently, there is a need for clinical data on the simultaneous treatment of major diagnostic features of rosacea. Therefore, an association of currently available efficacious and safe therapeutic agents may offer a comprehensive approach for the management of this complex disease with various possible phenotypes. Ivermectin 1% (IVM) cream and brimonidine 0.33% (BR) gel have been shown to be effective against papules/pustules and persistent facial erythema, respectively. IVM is a macrocyclic lactone derivative with dual anti-inflammatory and anti-parasitic properties.¹⁹⁻²⁵ Studies have demonstrated superiority of IVM over vehicle and metronidazole 0.75% cream in adults with moderate to severe papulopustular rosacea.^{26,27} BR is a highly selective alpha-2-adrenergic receptor agonist thus, a potent topical vasoconstrictive agent.²⁸⁻³¹ The efficacy, rapid onset of action, and safety of BR have been shown in studies including patients with moderate to severe persistent facial erythema, even with prolonged treatment (12 months).³²⁻³⁴ The maximal effect of BR on erythema is observable within 3 hours of application. However, BR has been associated with temporary worsening of erythema in some cases after initial application.³⁵ These therapeutic agents have demonstrable efficacy on different rosacea features. Therefore, it is important to investigate the association of IVM and BR topical treatments. The objective of this study was to evaluate the efficacy, safety, and patient satisfaction of IVM associated with BR (IVM+BR) compared to their respective vehicles in the treatment of moderate to severe rosacea, in an attempt to support a comprehensive approach to rosacea management. Moreover, the optimal timing of introducing BR to the association treatment was investigated.

MATERIALS AND METHODS

Study Design This multicenter, randomized, double-blind, vehicle-controlled, and parallel-group comparison study included subjects aged ≥ 18 years with moderate to severe rosacea (investigator global assessment [IGA] 3-4), characterized by persistent diffuse moderate to severe facial erythema (clinician erythema assessment [CEA] 3-4) and inflammatory lesions (15-70 papules/pustules). The study duration was 12 weeks and included 4 visits: baseline and weeks 4, 8, and 12. This study was conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practices, and in compliance with local regulatory requirements. It was approved by institutional review boards, and all subjects provided written informed consent prior to study procedures. **Treatments** All eligible subjects were randomized in a 1:1:2 ratio into two active and one double-vehicle treatment groups as described below: • IVM+BR active group: Half of the subjects received once-daily BR gel in the morning and once-daily IVM cream in the evening for 12 weeks (IVM+BR/12 weeks subgroup). - The other half of the subjects received once-daily BR vehicle gel in the morning for the first 4 weeks followed by once-daily BR gel for the remaining 8 weeks, and once-daily IVM cream in the evening for 12 weeks (IVM+BR/8 weeks subgroup). • Vehicle group: Subjects received once-daily BR vehicle gel in the morning and once-daily IVM vehicle cream in the evening for 12 weeks. All subjects received and were required to use daily, products for general skin care including a gentle skin cleanser, moisturizing lotion, and moisturizer SPF 15 sunscreen, as recommended by experts and guidelines.^{16,36,37} **Efficacy and Safety Endpoints** The primary endpoint was IGA success (clear/almost clear; overall assessment including background erythema and inflammatory lesions)²⁶ at week 12/hour 3 (3 hours after BR application), to demonstrate superiority of IVM+BR versus vehicle. Secondary efficacy endpoints included IGA at each visit; CEA (evaluation of erythema severity at each visit prior to and 3 hours after application of BR or its vehicle) and percent change from baseline in inflammatory lesion counts, to demonstrate the impact of the association on each major feature of rosacea; subject global improvement of rosacea and subject facial appearance satisfaction questionnaire. Safety assessment included monitoring the incidence of adverse events (AEs) throughout the study. **Sample Size and Randomization** There are no previous studies conducted with the concomitant use of IVM and BR. Therefore, the sample size of this study was calculated using previous IVM studies. A randomization list was generated by a statistician and the

RANUNI routine of the Statistical Analysis System (SAS®, SAS Institute Inc., Cary, NC, USA) was used for kit number generation.

FIGURE 1. Subject disposition.



Statistical Analysis Statistical analysis was performed in the intent-to-treat (ITT), per-protocol (PP), and safety (APT) populations. The primary efficacy endpoint was analyzed using the Cochran–Mantel–Haenszel (CMH, FREQ procedure from SAS®) statistical test, stratified by center after ridit transformation with the row mean difference statistics, testing the hypothesis of equality on the ITT/last observation carried forward (LOCF) population. PP analysis was also performed to assess the robustness of the results obtained on the ITT/LOCF population. Significance was declared at the 0.05 level. Secondary efficacy variables and questionnaires were analyzed in a similar manner as the primary analyses on the appropriate population. There was no adjustment of the type I error.

RESULTS

Subject Disposition The study was conducted from December 2015 to September 2016. A total of 190 subjects (95 subjects per group) enrolled at 26 sites in the United States and Canada. Of those, 171 (90%) completed the study (Figure 1). Subjects were predominantly Caucasian (91.1%) and female (72.1%), with a mean age of 49.5 years and a history of chronic rosacea > 5 years (70%). Demographic and baseline disease characteristics were similar in the two treatment groups (Table 1). The majority of subjects had moderate IGA/CEA at baseline (81.6% for both) and an average of 30 inflammatory lesions. **Efficacy/Investigator global assessment (IGA success) at week 12/hour 3** According to IGA at week 12/hour 3, more subjects in the total active group attained success (clear/almost clear) compared to the vehicle group in the ITT/LOCF (55.8% vs. 36.8%, respectively, P equals 0.007) (Figure 2A) and PP (62.5% vs. 39%, P equals 0.003) populations. An advantage for patients receiving BR from day 1 was observed, with the IVM+BR/12 weeks subgroup showing superior efficacy compared to vehicle (61.2% vs. 36.8%, P equals 0.003 in the ITT/LOCF population; and 68.3% vs. 39%, P equals 0.001 in the PP population) at the end of the study. The IVM+BR/8 weeks subgroup was numerically better than vehicle (50% vs. 36.8%, P equals 0.135 in the ITT/LOCF population; and 56.4% vs. 39%, P equals 0.096 in the PP population). At week 12, comparison of the effect of BR before and after application showed that, in the IVM+BR/12 weeks subgroup, the success rate almost doubled (from 32.7% to 61.2% at hour 0 and hour 3, respectively). In the IVM+BR/8 weeks subgroup, the success rate at hour 0 and hour 3 was 28.3% versus 50%, respectively (Figure 2B). **Investigator global assessment at each visit/hour 3** IGA at each visit demonstrated an onset of effect as early as week 4, with reported IGA success of 22.4%, 13%, and 9.5% in the IVM+BR/12 weeks, IVM+BR/8 weeks (ie, 4 weeks of BR vehicle at that point), and vehicle groups, respectively. The difference in the IVM+BR/12 weeks group versus vehicle (ie, 12.9%) reached statistical significance as early as week 4 (P equals 0.04) and remained significant until the end of treatment (P equals 0.02 at week 8 and P equals 0.003 at week 12; Figure 2C). **Clinician erythema assessment at week 12/hour 3** CEA showed statistically significant improvement in the IVM+BR/12 weeks and IVM+BR/8 weeks subgroups compared to the vehicle group (P less than 0.01). The rate of clear/almost clear, according to CEA, in the IVM+BR/12 weeks, IVM+BR/8 weeks, and

vehicle groups at week 12/hour 3 was 75.0%, 68.3%, and 40.7%, respectively (Figure 3). **Percent change**

in inflammatory lesion counts at week 12/hour 3 Median percent change in inflammatory lesion counts showed statistically significant improvement in the IVM+BR/12 weeks and IVM+BR/8 weeks subgroups compared to vehicle (78.3% vs. 65.5% [P less than 0.001] and 75.8% vs. 65.5% [P less than 0.01], respectively; Figure 4A). Moreover, the proportion of subjects who reached 100% reduction of inflammatory lesions was 16.3%, 6.5%, and 4.2% in the IVM+BR/12 weeks, IVM+BR/8 weeks, and vehicle groups, respectively. The difference of IVM+BR/12 weeks versus vehicle was statistically significant (P equals 0.015) in the ITT/LOCF population (Figure 4B). **Subject-reported Outcome** *Subject global improvement of rosacea* At the last visit (week 12/hour 3), the difference in improvement was statistically significant in the IVM+BR/12 weeks subgroup compared to the vehicle group (P equals 0.012), whereas it did not reach statistical significance in the IVM+BR/8 weeks subgroup. The rate of excellent and good improvement was 77.7%, 66.7%, and 55.2% in the IVM+BR/12 weeks, IVM+BR/8 weeks, and vehicle groups, respectively (ITT/LOCF population).

FIGURE 2. Investigator global assessment success (ITT-LOCF): (A) at week 12/hour 3; (B) at week 12/hour 0 versus week 12/hour 3 (ie, before vs. after application of BR); (C) Early onset of effect: IVM+BR/12 weeks versus vehicle.

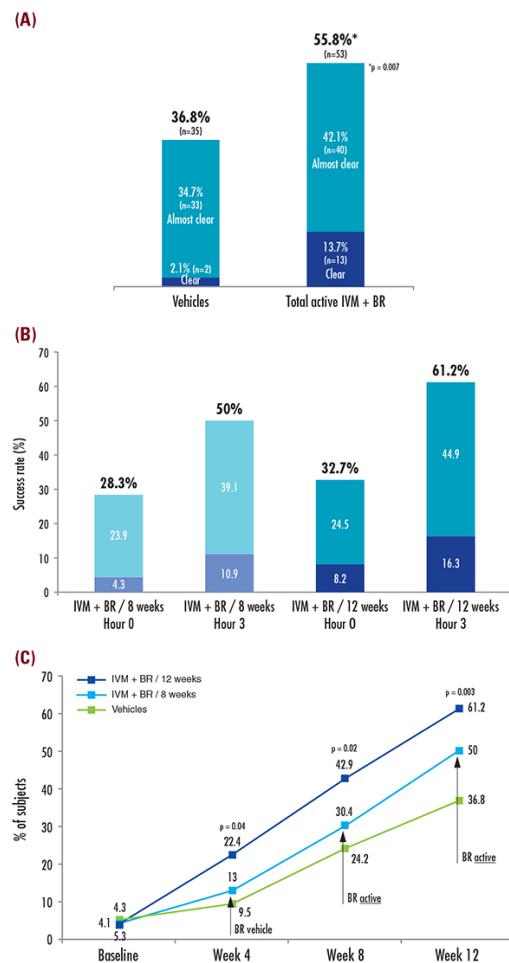
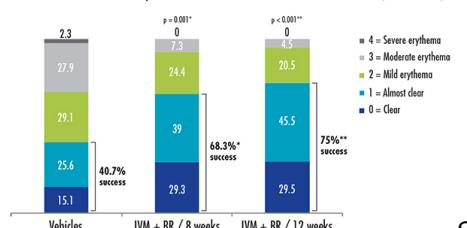


FIGURE 3. Clinician erythema assessment at week 12/hour 3 (ITT-LOCF).



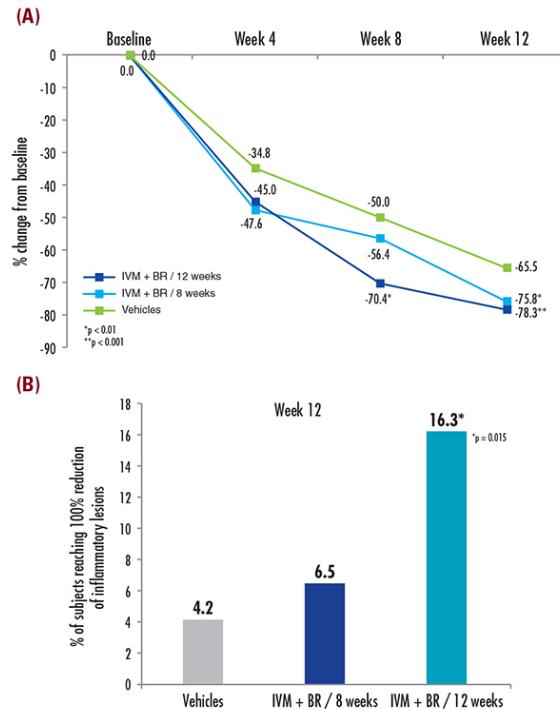
Subject facial appearance satisfaction After 4 weeks of IVM+BR treatment, the proportion of subjects who reported that bumps/pimples had become more visible since baseline was 27.7% in the IVM+BR/12 weeks subgroup and 18.6% in the IVM+BR/8 weeks subgroup (ie,

after 4 weeks of BR vehicle at that point). However, the overall subject facial appearance satisfaction (very satisfied/satisfied) after 4 weeks was similar between the IVM+BR/12 weeks (31.9%) and IVM+BR/8 weeks (27.9%) subgroups, suggesting that this prominence of bumps/pimples during treatment did not affect overall satisfaction nor resulted in treatment discontinuation. **Safety** Only 8 treatment-related AEs in 6 subjects (3.2%) were reported in this study. All AEs were dermatological in nature. Of those, 5 AEs (allergic dermatitis, erythema [2 AEs], skin burning sensation, and skin irritation) in 4 subjects (4.2%) and 3 AEs (erythema, pruritus, and rosacea) in 2 subjects (2.1%) were reported in the IVM+BR and vehicle groups, respectively. Related worsening of rosacea accounted for 1 AE in the IVM+BR group and all 3 related AEs in the vehicle group. No serious or severe related AEs were reported in this study. One related AE leading to discontinuation (allergic chest dermatitis) was reported in the IVM+BR group.

DISCUSSION

This was the first randomized clinical study investigating the concomitant use of IVM and BR for the treatment of inflammatory lesions and persistent centrofacial erythema of rosacea. The aim of the study was to assess the impact of these therapeutic agents within an integrated approach to treat rosacea symptoms, and examine two different regimens of treatment initiation over 12 weeks. In order to explore different treatment introduction sequences within the association, the IVM+BR group was split into two active subgroups: one with IVM and BR introduced jointly from baseline and another with BR introduced only after 4 weeks of BR vehicle along with IVM application. The subjects in the comparator vehicle group received both the vehicles of IVM and BR from the first day until the end of the study. The vehicle-controlled design of this study provided insight into the time of onset of treatment effect and the tolerability profile of the association, as well as the impact of these different regimens on subject satisfaction after 4 weeks of treatment.

FIGURE 4. Inflammatory lesion counts (ITT-LOCF): (A) Median percent change from baseline; (B) Percentage of subjects reaching 100% lesion reduction compared to baseline.



The combined approach showed superior efficacy in the total active group versus vehicle (55.8% vs. 36.8%) after 12 weeks of treatment, with a very low rate of worsening events. The success rate observed in the vehicle group highlights the importance of a comprehensive skin care regimen in support of the treatment. Efficacy findings were confirmed by the results of the IGA, CEA, and change in inflammatory lesion counts (Figure 5). Early administration of BR from the first day of treatment initiation exerts additional benefit compared to the 4-week delayed introduction, with more subjects achieving clear/almost clear in the 12-week subgroup. The additive effect of BR to IVM treatment in IGA success was demonstrated in both IVM+BR subgroups and was confirmed by a better efficacy in erythema (CEA success) and a reduction of inflammatory lesions. Of note, early introduction of BR showed a

trend toward better efficacy in all assessments compared to delayed introduction. It is known that patients expect a quick onset of action by therapeutic agents.³⁸ The early onset of effect induced by the association at week 4 offered an advantage that was maintained until the end of treatment, especially in the IVM+BR/12 weeks subgroup. Furthermore, the lower incidence of treatment-related AEs (similar to the vehicle group of this study ie, 4.2% vs. 2.1%, respectively), in comparison to monotherapy with BR (approximately 10%)³³, suggests a safety benefit from this combined approach. Therefore, concomitant administration of these two therapeutic agents as early as possible may maximize the chance of treatment success, and improve adherence and safety. In addition, success rates for the active treatments continued to increase throughout the study. This emphasizes the option to potentially continue treatment beyond the endpoint of the study (12 weeks) to reach maximal efficacy (with the potential of even more subjects clear on the IGA scale). Subject assessment of global improvement of rosacea corroborated investigator efficacy findings, indicating greater improvement in the active subgroups than in the vehicle group. As expected, more subjects reported noticing inflammatory lesions in the IVM+BR/12 weeks subgroup than in the IVM+BR/8 weeks subgroup after 4 weeks of treatment. However, this did not affect subject facial appearance satisfaction, with similar rates reported in both subgroups (31.9% vs. 27.9%, respectively). Of note, following the application of BR, symptoms such as telangiectasia may appear more pronounced. The management of these symptoms ought to be addressed by other tailored treatments and is beyond the scope of this investigation. The association of IVM and BR was well tolerated regardless of the time of BR introduction in the treatment regimen (day 1 or week 4) and comparable throughout all study groups. The incidence of related AEs was less than 5%. In the active groups, only 1 case of worsening of rosacea (increased facial erythema) and 1 AE leading to discontinuation (allergic chest dermatitis during the first month, while the subject was still under BR vehicle) were reported in the IVM+BR/8 weeks subgroup. In addition, incorporating a complete and intensive skin care regimen as recommended^{15,18,39}, including cleanser, moisturizing lotion, and daily sun protection may have improved benefit for the restoration of the skin barrier function (as observed across all treatment groups), resulting in overall improved tolerability and fewer side effects.

In conclusion, the concomitant use of IVM 1% cream with BR 0.33% gel demonstrated superior efficacy and a comparable safety profile versus vehicle for the treatment of moderate to severe rosacea. Early introduction of BR from the first day of treatment, along with a complete daily skin care regimen, may accelerate treatment success without impairing patient satisfaction or tolerability. This association regimen is a promising option for the comprehensive management of this complex disease.

DISCLOSURES

Dr Linda Stein Gold is an investigator, consultant and speaker for Galderma. Dr Kim Papp is a consultant, speaker, advisory board member, and investigator for Galderma. Dr Charles

FIGURE 5. Subject photographs (investigator global assessment and lesion counts) at baseline and week 12 from the IVM+BR/12 weeks subgroup.



Lynde has been a consultant, principal investigator, and speaker for Galderma. Dr Edward Lain is a consultant and investigator for Galderma. Dr Melinda Gooderham has been an investigator, speaker, and advisory board member for Galderma. Dr Sandra Johnson is an investigator, speaker, and consultant for Galderma. Mr Nabil Kerrouche is an employee of Galderma.

ACKNOWLEDGMENTS

The authors thank Sotirios Georgantopoulos PhD (SG Medical Writing B.V.) for editorial assistance.

REFERENCES

1. Wilkin J, Dahl M, Detmar M, et al. Standard grading system for rosacea: report of the National Rosacea Society Expert Committee on the classification and staging of rosacea. *J Am Acad Dermatol.* 2004;50:907-912.
2. Tan J, Berg M. Rosacea: current state of epidemiology. *J Am Acad Dermatol.* 2013;69(6 Suppl 1):S27-35.
3. Culp B, Scheinfeld N. Rosacea: a review. *P T.* 2009;34:38-45.
4. Korting HC, Schöllmann C. Current topical and systemic approaches to treatment of rosacea. *J Eur Acad Dermatol Venereol.* 2009;23:876-882.
5. Powell FC. Clinical practice. Rosacea. *N Engl J Med.* 2005;352:793-803.
6. Tan J, Schöfer H, Araviiskaia E, et al. Prevalence of rosacea in the general population of Germany and Russia - The RISE study. *J Eur Acad Dermatol Venereol.* 2016;30:428-434.
7. Crawford GH, Pelle MT, James WD. Rosacea: I. Etiology, pathogenesis, and subtype classification. *J Am Acad Dermatol.* 2004;51:327-341.
8. Pelle MT, Crawford GH, James WD. Rosacea: II. Therapy. *J Am Acad Dermatol.* 2004;51:499-512.
9. Dirschka T, Micali G, Papadopoulos L, et al. Perceptions on the psychological impact of facial erythema associated with rosacea: Results of international survey. *Dermatol Ther (Heidelb).* 2015;5:117-127.
10. Forton F, Germaux MA, Brasseur T, et al. Demodicosis and rosacea: epidemiology and significance in daily dermatologic practice. *J Am Acad Dermatol.* 2005;52:74-87.
11. Buechner SA. Rosacea: an update. *Dermatology.* 2005;210:100-108.
12. Wilkin JK, DeWitt S. Treatment of rosacea: topical clindamycin versus oral tetracycline. *Int J Dermatol.* 1993;32:65-67.
13. Casas C, Paul C, Lahfa M, et al. Quantification of Demodex folliculorum by PCR in rosacea and its relationship to skin innate immune activation. *Exp Dermatol.* 2012;21:906-910.
14. Forton FM, De Maertelaer V. Two consecutive standardized skin surface biopsies: An improved sampling method to evaluate demodex density as a diagnostic tool for rosacea and demodicosis. *Acta Derm Venereol.* 2017;97:242-248.
15. Tan J, Almeida L, Bewley A, et al. Updating the diagnosis, classification and assessment of rosacea: Recommendations from the global ROSacea COnsensus (ROSCO) panel. *Br J Dermatol.* 2016;176:431-438.
16. Schaller M, Almeida L, Bewley A, et al. Rosacea treatment update: Recommendations from the global ROSacea COnsensus (ROSCO) panel. *Br J Dermatol.* 2016;176:465-471.
17. Tan J, Steinhoff M, Berg M, et al. Shortcomings in rosacea diagnosis and classification. *Br J Dermatol.* 2017;176:197-199.
18. Del Rosso JQ, Thiboutot D, Gallo R, et al. Consensus recommendations from the American Acne & Rosacea Society on the management of rosacea, part 1: a status report on the disease state, general measures, and adjunctive skin care. *Cutis.* 2013;92:234-240.
19. Shimose L, Munoz-Price LS. Diagnosis, prevention, and treatment of scabies. *Curr Infect Dis Rep.* 2013;15:426-431.

20. Pariser DM, Meinking TL, Bell M, Ryan WG. Topical 0.5% ivermectin lotion for treatment of head lice. *N Engl J Med.* 2012;367:1687-1693.
21. Damian D. Demodex infestation in a child with leukemia: treatment with ivermectin and permethrin. *Int J Dermatol.* 2003;42:724-726.
22. Filho PA, Hazarbassanov RM, Grisolia AB, et al. The efficacy of oral ivermectin for the treatment of chronic blepharitis in patients tested positive for *Demodex* spp. *Br J Ophthalmol.* 2011;95:893-895.
23. Ci X, Li H, Yu Q, et al. Avermectin exerts anti-inflammatory effect by downregulating the nuclear transcription factor kappa-B and mitogen-activated protein kinase activation pathway. *Fundam Clin Pharmacol.* 2009;23:449-455.
24. Yanagihara K, Kadoto J, Kohno S. Diffuse panbronchiolitis-pathophysiology and treatment mechanisms. *Int J Antimicrob Agents.* 2001;18 Suppl 1:S83-87.
25. Ianaro A, Ialenti A, Maffia P, et al. Anti-inflammatory activity of macrolide antibiotics. *J Pharmacol Exp Ther.* 2000;292:156-163.
26. Stein L, Kircik L, Fowler J, et al. Efficacy and safety of ivermectin 1% cream in treatment of papulopustular rosacea: results of two randomized, double-blind, vehicle-controlled pivotal studies. *J Drugs Dermatol.* 2014;13:316-323.
27. Taieb A, Ortonne JP, 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.* 2015;172:1103-1110.
28. Rahman MQ, Ramaesh K, Montgomery DNI. Brimonidine for glaucoma. *Expert Opin Drug Saf.* 2010;9:483-491.
29. Katz LJ. Brimonidine tartrate 0.2% twice daily vs timolol 0.5% twice daily: 1-year results in glaucoma patients. Brimonidine study group. *Am J Ophthalmol.* 1999;127:20-26.
30. Serle JB. A comparison of the safety and efficacy of twice daily brimonidine 0.2% versus betaxolol 0.25% in subjects with elevated intraocular pressure. The brimonidine study group III. *Surv Ophthalmol.* 1996;41 (Suppl 1):S39-47.
31. Tanghetti EA, Jackson JM, Belasco KT, et al. Optimizing the use of topical brimonidine in rosacea management: panel recommendations. *J Drugs Dermatol.* 2015;14:33-40.
32. Fowler J, Jarratt M, Moore A, et al. Once-daily topical brimonidine tartrate gel 0.5% is a novel treatment for moderate to severe facial erythema of rosacea: results of two multicentre, randomized and vehicle-controlled studies. *Br J Dermatol.* 2012;166:633-641.
33. Fowler J Jr, Jackson M, Moore A, et al. Efficacy and safety of once-daily topical brimonidine tartrate gel 0.5% for the treatment of moderate to severe facial erythema of rosacea: results of two randomized, double-blind, and vehicle-controlled pivotal studies. *J Drugs Dermatol.* 2013;12:650-656.
34. Moore A, Kempers S, Murakawa G, et al. Long-term safety and efficacy of once-daily topical brimonidine tartrate gel 0.5% for the treatment of moderate to severe facial erythema of rosacea: results of a 1-year open-label study. *J Drugs Dermatol.* 2014;13:56-61.
35. Routt ET, Levitt JO. Rebound erythema and burning sensation from a new topical brimonidine tartrate gel 0.33%. *J Am Acad Dermatol.* 2014;70:e37-38.
36. Del Rosso JQ, Gallo RL, Tanghetti E, et al. An evaluation of potential correlations between pathophysiologic mechanisms, clinical manifestations, and management of rosacea. *Cutis.* 2013;91(3 Suppl):1-8.
37. Del Rosso JQ. Understanding skin cleansers and moisturizers: the correlation of formulation science with the art of clinical use. *Cosmetic Dermatology.* 2003;16:19-31.

38. Weinkle AP, Doktor V, Emer J. Update on the management of rosacea. *Clin Cosmet Investig Dermatol.* 2015;8:159-177.
39. Schaller M, Schöfer H, Homey B, et al. Rosacea Management: Update on general measures and topical treatment options. *J Dtsch Dermatol Ges.* 2016;14(Suppl 6):17-27.

AUTHOR CORRESPONDENCE

Linda Stein Gold MD

E-mail:..... STEIN1@hfhs.org