

# Treatment of Rosacea: Expert Insight on Trends and Best Practice

Linda Stein Gold MD

Department of Dermatology, Henry Ford Medical Center, Detroit, MI

**R**osacea is a chronic inflammatory disease that has been estimated to affect 16 million people in America alone.<sup>1</sup> It is characterized by a range of clinical symptoms notably erythema, telangiectasia, papules, pustules, plaques, edema, skin discomfort, phymatous changes and ocular involvement.<sup>2</sup> In addition to clinical symptoms, the condition is recognized to affect both social and professional lives and can lead to psychosocial issues.<sup>1</sup>

In clinical practice, patients often present with a specific range of symptoms, with one or two primary symptoms observed as the leading ones. For didactical reasons, the typical classifications outline certain rosacea "subtypes" (erythematotelangiectatic -ETR, papulopustular -PPR, phymatous -PHY and ocular -OR)<sup>2</sup> or subforms such as granulomatous rosacea and Morbus Morbihan.<sup>3</sup> When developing the treatment plan for an individual patient, we need to be careful not to try to fit a patient to a subtype, or fit treatment by subtype, but rather identify the leading symptom(s) and tailor the treatment plan to the individual's set of symptoms. This, in my experience, yields better patient outcomes.

This is an exciting time in the advancement of our understanding and treatment of rosacea, with further elucidation of the pathophysiology coupled with the development of new therapies to treat the disease. Inflammation is the key underlying mechanism, giving rise to the varying symptoms. New scientific data continues to demonstrate the involvement of infiltrates, changes in pro-inflammatory cytokine profile and gene upregulation, therefore raising the need for most patients to receive basic anti-inflammatory therapy.<sup>4</sup>

## Treatment of Inflammatory Lesions

Traditionally, there have been a limited number of treatment options for rosacea. Metronidazole, azelaic acid, and anti-inflammatory dose doxycycline (40 mg) have demonstrated efficacy for the treatment of PPR.<sup>5</sup> These drugs are effective and well tolerated but most rosacea patients are not completely clear and flares are common. Doxycycline (40 mg modified-release capsule once daily) is the only FDA approved oral treatment for the reduction of inflammatory lesions in rosacea and has demonstrated a reduction in lesions across all severities of rosacea, combined with a good safety profile.<sup>6,7</sup>

Ivermectin 1% cream has recently received FDA approval for the treatment of inflammatory lesions of rosacea.<sup>8</sup> In my clinic, we treated patients within the ivermectin clinical development program, and demonstrated that ivermectin is an efficacious topical treatment with a good safety profile for up to a year.<sup>9,10</sup> The safety profile was shown to be equal or even better than vehicle alone.<sup>9,10</sup> The majority of patients reported overall improvement following treatment as either excellent or good, and 53% felt their disease no longer had an effect on their overall quality of life.<sup>9,10</sup> The majority of patients reported overall improvement following treatment as either excellent or good, and 53% felt their disease no longer had an effect on their overall quality of life.<sup>9,10</sup> Ivermectin 1% cream has also demonstrated significant superiority in reduction of inflammatory lesions in patients with moderate to severe PPR compared to metronidazole 0.75% cream, the gold standard in inflammatory lesion treatment.<sup>11</sup>

## Treatment of Facial Erythema

Classified as a primary symptom<sup>2</sup>, facial erythema represents the reaction of facial skin to the ongoing histological and pathophysiological chronic inflammatory mechanisms underlying the disease.  $\alpha$ -1 and  $\alpha$ -2 adrenergic receptor agonists are under investigation for the treatment of erythema.<sup>13</sup> The  $\alpha$ -adrenergic receptor agonist brimonidine gel 0.33% is the first approved therapy for permanent erythema of rosacea<sup>12</sup>, and has now been in real-world clinical use for over a year addressing the redness that patients suffer. Patients who feel stigmatized or insecure with their appearance due to facial erythema can greatly benefit from brimonidine gel. Patients need to be made aware also that once their level of facial erythema has reduced, other symptoms, such as inflammatory lesions, can be more noticeable. A combination of clinical treatments can be considered to treat different symptoms concomitantly to attain the optimum results for the patient in such cases. Brimonidine gel has demonstrated good efficacy and safety profile in clinical trials and has been shown to be well tolerated in the presence of concomitant therapies for inflammatory lesions.<sup>13,14</sup> Currently, topical oxymetazoline hydrochloride cream, an  $\alpha$ -1 adrenergic receptor agonist and  $\alpha$ -2 adrenergic receptor partial agonist, is in clinical development.<sup>13</sup>

## Optimizing Treatment in Facial Erythema

Tanghetti et al recently explained how to set patient expectations and optimize treatment initiation to ultimately ensure the best results for the patient.<sup>15</sup> A well-educated patient will always be more compliant and show potentially better efficacy for treatments administered. Many patients are still unaware of all symptoms or triggers of rosacea. Issues arising from lack of awareness of rosacea can be helped with education around the condition, the importance of avoiding trigger factors, how best to apply topical treatments and what to expect from their treatments. For example, it is important to evaluate the patient for the presence of significant telangiectasia as these will become more noticeable when the background erythema is treated. In

my clinic, I clear the inflammatory lesions prior to starting treatment with brimonidine gel. Some physicians report that they treat symptoms concomitantly with a successful outcome.

In conclusion, initiating a more tailored approach for the treatment of specific symptoms rather than subtypes can help to ensure we provide the best results for our patients. Newly approved treatments, such as ivermectin 1% cream for the treatment of inflammatory lesions and brimonidine gel for the treatment of persistent erythema, will further strengthen the current armamentarium for this chronic disease.

### Disclosures

Dr. Stein Gold is an investigator for Galderma, Allergan, and Actavis, and an advisor for Galderma, Allergan, Valeant, Merz, and Actavis. Medical writing support was provided by Natasha Singh Kent PhD, Havas Life Medicom, and was funded by Galderma.

### References

- Baldwin H. Psychosocial implications of rosacea. *The Dermatologist*. 2012; Supplement:2-4.
- 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.
- Reinholz M, Tietze JK, Kilian K, et al. Rosacea S1 Guideline. *JDDG*. 2013;11(8):768-780.
- Buhl T, Sulk M, Nowak P, et al. Molecular and Morphological Characterization of Inflammatory Infiltrate in Rosacea reveals Activation of Th1/Th17 Pathways. *J Inv Dermatol*. 2015; In press
- van Zuuren EJ, Kramer S, Carter B, et al. Interventions for rosacea. *Cochrane Database Syst Rev*. 2011(3):CD003262.
- Del Rosso JQ, Webster GF, Jackson M, et al. Two randomized phase III clinical trials evaluating anti-inflammatory dose doxycycline (40-mg doxycycline, USP capsules) administered once daily for treatment of rosacea. *J Am Acad Dermatol*. 2007;56(5):791-802.
- Oracea® Prescribing Information. Available at: <http://www.galdermausa.com/PI/OraceaPI.pdf>. Accessed 1 April 2015.
- Soolantra® Prescribing Information. Available at: <http://www.galdermausa.com/pi/soolantrapi.pdf>. Accessed 1 April 2015.
- Stein Gold 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(3):316-23.
- 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):1380-6.
- Taieb A, Ortonne JP, et al; Ivermectin Phase III study group. 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;172:1103-1100.
- Galderma Laboratories LP. Mirvaso® (brimonidine) 0.33% topical gel package insert. Available at: [http://www.accessdata.fda.gov/drugsatfda\\_docs/label/2013/2047081bl.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/2047081bl.pdf).
- 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(6):650-6.
- 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-labeled study. *J Drugs Dermatol* 2014;13(1):56-61.
- Tanghetti EA, Jackson JM, Belasco KT, et al. Optimizing the use of topical brimonidine in rosacea management: panel recommendations. *J Drugs Dermatol*. 2015;14(1):33-40.

© 2015-Journal of Drugs in Dermatology. All Rights Reserved.

This document contains proprietary information, images and marks of Journal of Drugs in Dermatology (JDD).

No reproduction or use of any portion of the contents of these materials may be made without the express written consent of JDD.

If you feel you have obtained this copy illegally, please contact JDD immediately.

### AUTHOR CORRESPONDENCE

**Linda Stein Gold MD**

E-mail:..... lstein1@hfhs.org