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Clinical Evidence. Practical Advice

Editor-in-Chief: Dr. Stuart Maddin

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Dr. Stuart Maddin is the Chairman of SkinCareGuide. He is one of North America's leading dermatologists and the author of numerous dermatologic journal articles, monographs and textbooks. In addition to providing consultative input to a number of pharmaceutical and biotech companies, he is the director of the Clinical Trials Unit at the Department of Dermatology and Skin Science, University of British Columbia. Dr. Maddin has also acted in an advisory capacity to a number of drug regulatory agencies, such as the Health Protection Branch (Ottawa), the AAD-FDA Liaison Committee, and World Health Organization (Geneva). He is the founder of the Dermatology Update symposia, now in its 29th year. As well, he is Past President of the Canadian Dermatology Association and served as Secretary-General of the International Committee of Dermatology – International League of Dermatological Societies.

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Rosacea: An Update on Medical Therapies

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Introduction

Rosacea is a common, chronic cutaneous condition that affects the face. Several topical medications are currently approved for the treatment of rosacea, including azelaic acid and metronidazole. Systemic therapy utilizing a sub-antimicrobial dose of doxycycline is also effective in treating rosacea. Identification of subtypes can help guide treatment strategies. Psychosocial implications of rosacea must be considered and conservative management, such as skin care, must form an important part of the overall care. Recently, new insights into the pathophysiology of rosacea have led to the emergence of etiologically oriented treatments, including the newly approved brimonidine gel 0.33% (Onreltea™).

Background

- Rosacea is a common chronic cutaneous condition that primarily affects the central facial area, including the cheeks, nose, eyes, chin and forehead.[1]
- Primary cutaneous manifestations include sensitive skin, flushing, persistent erythema, papules, pustules and telangiectases.
- Although symptoms may wax and wane in the short-term, rosacea is slowly progressive in the long-term for many patients.[2]
- The National Rosacea Society has classified rosacea into four main subtypes: [3]
  1. Erythematotelangiectatic
  2. Papulopustular
  3. Phymatous
  4. Ocular
- Progression from one subtype to another is possible.[4] Proper identification of subtypes may help guide therapeutic strategies.
- Rosacea affects up to 10% of the general population and the onset is typically between the ages of 30 and 50 years.[5]
- It is especially common in light-skinned individuals of northern European descent, with women more frequently affected.[5,6] However, men are more prone to develop thickening and distorting phymatous skin changes, especially of the nose.
- While rosacea was considered rare in people of colour, a recent increase in case reports documenting rosacea in patients with Fitzpatrick Skin Types IV-VI, suggests that it is more common in darker skinned individuals than previously thought, and may have been under-recognized and unreported in the dermatology literature.[7,8]
- Rosacea pathophysiology is multifactorial and currently not fully understood. Factors proposed to play a role include vascular abnormalities, gastrointestinal disorders, matrix

degeneration, pilosebaceous gland abnormalities, microbial activity, and altered innate immune response.[9,10]
- Rosacea can create psychosocial burdens, such as embarrassment, anxiety and low self-esteem, and adversely affect quality-of-life, which should be taken into consideration when treating these patients.[11,12] Conservative measures, such as trigger avoidance, proper skin care, camouflaging cosmetics, and photo-protection should also be incorporated into the management plan.[13]

Conventional Therapies

Topical Metronidazole

- Metronidazole (Noritate® 1% Cream, Dermik; MetroGel 1%, Metrocream™ 0.75% Cream, Metrolotion® 0.75% Lotion, Metrogel® 0.75% gel), first demonstrated efficacy against rosacea in the 1980s.[14]
- Despite being an antibacterial and antiprotozoal agent, metronidazole confers its therapeutic efficacy mostly through its anti-inflammatory and antioxidant effects.[15]
- Multiple trials have demonstrated that topical metronidazole significantly decreases the number of inflammatory lesions and reduces erythema compared to placebo; is generally well tolerated; has a low incidence of adverse effects; and is effective in maintaining remission.[16-19]
- Importantly, different formulations of metronidazole have demonstrated similar efficacy, regardless of vehicle type (cream, gel, or lotion) or concentration (0.75% or 1%).[20,22]
- Once- and twice-daily applications have similar efficacy.[20,23]
- Metronidazole 1% has demonstrated less cumulative potential for irritation over a 21-day period, (similar to that of white petrolatum) compared with metronidazole gel 0.75%.[24]
- When combined with sunscreen SPF 15, metronidazole may reduce development of facial telangiectasia.[25]
- Topical metronidazole is a pregnancy category B medication.

Topical Azelaic Acid

- Azelaic acid (Finacea®) is a naturally occurring dicarboxylic acid approved in the last decade for the treatment of mild to moderate rosacea.[26]
- Mostly applied as a 15% gel or a 20% cream, azelaic acid has anti-inflammatory, antikeratinizing, and antibacterial effects.[26]
- Multiple trials have demonstrated that azelaic acid is more effective than placebo at reducing the number of inflammatory lesions and degree of erythema.[27-29] The pooled rates of patients showing marked improvements with azelaic acid treatment were 70-80%, compared to 50-55% with placebo.[30]
- Azelaic acid also has a relatively low incidence of adverse effects, with burning, stinging and irritation being the most commonly reported.[28] However, data from Colon et al, show that azelaic acid gel 15% caused significantly more irritation than white petrolatum when administered over a 21-day period, as well as both concentrations of metronidazole ($p<.0001$ for all comparisons).[24]
- Although the conventional regimen is twice-daily application, once-daily dosing has been found to be equally effective.[31]
- Further studies are needed to support the use of azelaic acid as a maintenance therapy.[30]
- It is currently a pregnancy B category medication.

Tetracycline

- While not indicated for the treatment of rosacea, oral antibiotics have been recognized for the past 50 years as an effective treatment and are thought to exert their therapeutic effects primarily via anti-inflammatory rather than antibacterial mechanisms.[32]
- Because the role of micro-organisms in rosacea pathogenesis remains unclear, the use of antibiotics at standard doses is not an ideal approach.
- However, the tetracycline-family of antibiotics is effective in treating ocular rosacea, which typically affects greater than 50% of patients with rosacea.
- Tetracyclines are the most frequently used class of antibiotics with greatest efficacy against inflammatory papules and pustules.
- Tetracyclines are contraindicated in pregnant women.
- Second-generation tetracyclines, including minocycline and in particular doxycycline, are especially safe and effective oral therapies for rosacea.
- Unlike the parent, second generation tetracyclines have greater bioavailability, rapid onset of action, and can be taken with food, which minimizes gastrointestinal side effects.[33]
- Second-generation tetracyclines require once-daily dosage, which may improve compliance.
- Most importantly, they are effective at a sub-antimicrobial dose, which avoids disruption of the endogenous flora and, of global importance, the propagation of antibacterial resistance.[34]
- Recently, two phase 3, multicenter, randomized, double-blind, placebo-controlled clinical trials demonstrated that a daily sub-antimicrobial dose of 40 mg doxycycline (Apprilon™), administered to patients with moderate to severe rosacea, significantly reduced total inflammatory papule and pustule counts compared with placebo after 16-weeks treatment, with significant improvements evident at 3 weeks.[34]
- Prevalence of adverse effects was low and only marginally higher than placebo, with nasopharyngitis (4.8%), diarrhea (4.4%) and headaches (4.4%) being the most commonly reported.
- No cases of photosensitivity or vaginal candidiasis occurred.
- A separate study demonstrated that the effectiveness of 40 mg doxycycline is comparable to that of 100 mg doxycycline in rosacea but with a lower incidence of gastrointestinal side effects.[35]

New Therapies

Brimonidine

- Diffuse facial erythema has long posed an unmet need in rosacea management.[5]
- One contributing factor is abnormal cutaneous vasomotor responses, which leads to persistently enlarged facial blood vessels.[36] These blood vessels remain responsive to vasoactive stimuli, hence the growing interest in α2-

adrenergic receptor agonists as a possible therapeutic option.[36]

- Brimonidine 0.33% gel (Mirvaso™), approved by FDA in August 2013, is the latest addition to the therapeutic armamentarium and the first topical agent approved for the treatment of facial erythema of rosacea. This formulation was recently approved by Health Canada with the trade name Onreltea®, for the topical treatment of facial erythema of rosacea in adults 18 years of age or older.[12] *(*Note- the literature refers to both brimonidine gel 0.33% and brimonidine tartrate gel 0.5%. This is the same product and the terms are interchangeable.)*
- Brimonidine is a highly selective α2-adrenergic receptor agonist with potent vasoconstrictive activity and is also found in prescription eye drops for the treatment of glaucoma.[37]
- In two phase 3 randomized, double-blind pivotal trials, topical brimonidine tartrate gel 0.5% once daily was significantly more effective than vehicle over a 4-week treatment period.[38] In the two trials, approximately 24.82% of the patients using brimonidine tartrate gel 0.5% versus (vs.) 9.76%; $p<0.05$) on day 29 were assessed to have at least a two-grade improvement by both clinicians and patients over 12 hours after drug application, with peak improvements observed at 3 and 6 hours (Fig. 1 and 2).
- Noticeable improvement (one-grade Clinician's Erythema Assessment and 5 point Patient Self Assessessment Scale) was observed (28.2% vs. 5.9%; $p<0.01$) as early as 30 minutes after the first application on day one.
- Adverse events were mildly elevated in the treatment group but were largely cutaneous, transient and mild, with the most commonly reported being worsening of erythema (5.1%), pruritus (5.0%), skin irritation (1.2%), and rosacea (1.1%).
- There was no evidence of tachyphylaxis, rebound, or aggravation of telangiectasia or inflammatory lesions.
- Data from a 12-month, multi-center, open-label study also show no incidence of tachyphylaxis, with efficacy maintained over the long-term.[39]

Other Therapies

- Topical sodium sulfacetamide 10% with sulfur 5% has been used for over 50 years for its clinical efficacy and safety in the treatment of rosacea, although its mechanism of action is not well understood.
- In an 8-week study, sulfacetamide 10% with sulfur 5% has been shown to significantly reduce inflammatory lesions (78% vs. 36%; $p<0.001$) and facial erythema (83% vs. 31%; $p<0.001$) compared to vehicle.[4,40] Studies evaluating this therapy, however, are limited and generally of poor quality.[30]
- Laser and light therapies have been used successfully for many years to treat the vascular manifestations of rosacea.
- In a randomized, controlled, single-blind, split-face trial, both pulsed dye laser and intense pulse light were found to be effective, with similar efficacy in reducing erythema and telangiectasia in patients with erythematotelangiectatic rosacea.[41]

Conclusion

Therapeutic decision-making in the treatment of rosacea should be guided by high-level evidence, where available, and will depend on subtype, severity, patient expectations, tolerance, budget and previous therapy used. Topical azelaic acid and metronidazole are considered safe and efficacious first-line therapies. A sub-antimicrobial dose of doxycycline is the best research-supported oral therapeutic indicated for the treatment of rosacea and provides a safe and convenient option

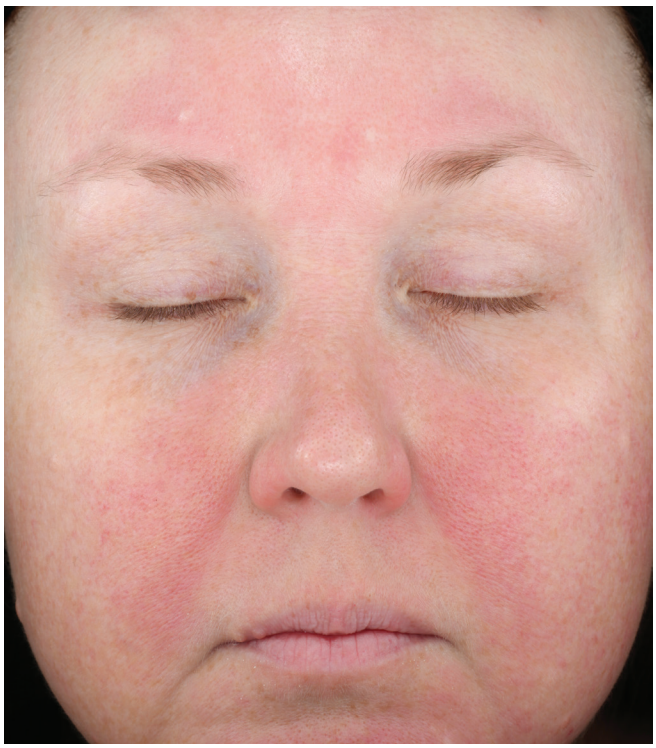

Figure 1. Baseline

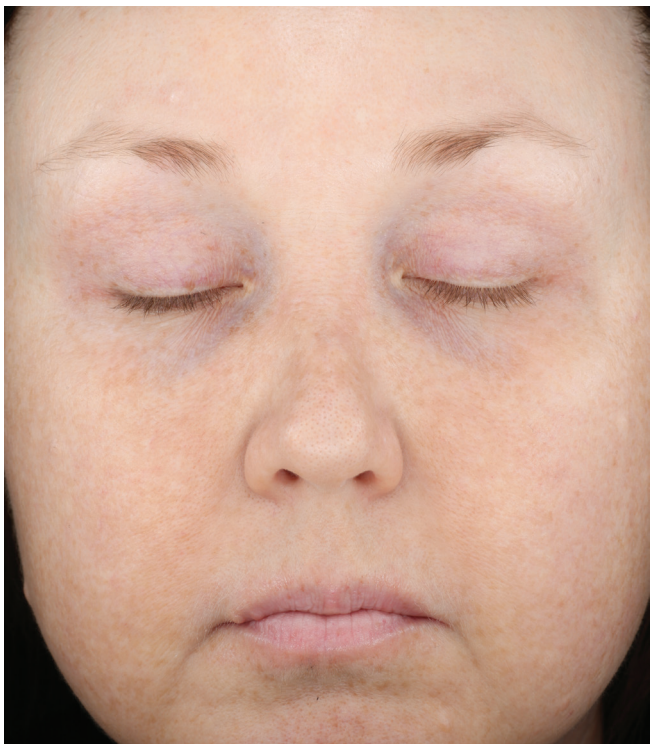

Figure 2. 3 hours post-Brimonidine treatment

for patients who prefer oral to topical therapy. Light and laser-based therapies play a major clinical role in the treatment of the telangiectatic component. The promising novel therapy, brimonidine, fills a much-needed niche in the targeted treatment of facial diffuse erythema of rosacea.

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