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Authors

Del Rosso, James Q
Tanghetti, Emil
Webster, Guy
et al.

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CONSENSUS

Update on the Management of Rosacea from the American Acne & Rosacea Society (AARS)

by JAMES Q. DEL ROSSO, DO, FAOCD, FAAD; EMIL TANGHETTI, MD, FAAD; GUY WEBSTER, MD, PhD, FAAD; LINDA STEIN GOLD, MD, FAAD; DIANE THIBOUTOT, MD, FAAD; and RICHARD L. GALLO, MD, PhD, FAAD

Dr. Del Rosso is Adjunct Clinical Professor of Dermatology at Touro University, Nevada in Henderson, Nevada; and Research Director at JDR Dermatology Research, Clinical Dermatology, Thomas Dermatology in Las Vegas, Nevada. Dr. Tanghetti is with the Center for Dermatology and Laser Surgery in Sacramento, California. Dr. Webster is with Jefferson Medical College in Hockessin, Delaware. Dr. Stein Gold is the Director of Dermatology, Clinical Research, and Division Head of Dermatology at Henry Ford Health System in Detroit and West Bloomfield, Michigan. Dr. Thiboutot is Professor of Dermatology at Penn State University College of Medicine in Hershey, Pennsylvania. Dr. Gallo is Chief, Division of Dermatology, and Professor of Medicine and Pediatrics at the University of California, San Diego in San Diego, California.

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ABSTRACT

Importance: Previous consensus articles on rosacea from the American Acne and Rosacea Society (AARS) have focused on pathophysiology, clinical assessment based on phenotypic expressions of rosacea, management guidelines, discussions of individual medical therapies, and reviews of physical modalities. Pathophysiologic mechanisms believed to be operative in rosacea have been covered extensively in the literature. **Objective:** This article updates the previously published consensus recommendations from the AARS on the management of rosacea, including systematic literature and evidence-based reviews of available therapeutic agents and physical modalities. **Observations:** This article includes discussions of available published data on topical ivermectin, topical oxymetazoline, combination therapy approaches, and physical devices for the management of rosacea. Consistent with what many publications on rosacea currently emphasize, clinicians are encouraged to define the clinical manifestations present in the patient and to select therapies that correlate with the optimal treatment of those manifestations. There are less data available on how to optimally integrate therapies; however, it appears that rationally selected medical therapies can be utilized concurrently. **Conclusion:** Due to the multifactorial pathogenesis of rosacea, its clinical presentation is heterogeneous. Rosacea is a chronic and recurrent inflammatory disorder, and clinical manifestations often vary in nature and severity over time, which might necessitate an adjustment in treatment. As new data become available, rosacea management approaches should be updated.

KEYWORDS: Rosacea, inflammation, erythema, alpha-agonist

Recognized as one of the most common and clinically characteristic facial skin disorders, rosacea is an inflammatory dermatosis with a reported prevalence of at least 10 percent among Caucasian adults; it also affects several other racial groups, including Latin-American, African-American, African, and Asian people.[1–4] The diagnosis of rosacea is made clinically, based on visible assessment and patient history, after other causes of facial erythema and/or papulopustular skin lesions have been excluded,[2,5] including contact dermatitis, seborrheic dermatitis, photodamage, acne vulgaris, cutaneous lupus, and carcinoid syndrome.

The classification of rosacea in both clinical practice and research previously utilized subtype designations as described by Wilkin et al in 2002[5] from the National Rosacea Society. However, the current recommendations from multiple organizations with interest in the diagnosis and treatment of rosacea suggest characterizing patients with rosacea by individual clinical manifestations and symptoms that are present at the time of examination.[2,6–8] As rosacea is a phenotypically heterogeneous disease, this might include central facial erythema without papulopustular (PP) lesions; central facial erythema with PP lesions; the presence of phymatous changes, ocular signs, and symptoms; extensive presence of facial telangiectasias; and marked, persistent, nontransient facial erythema that remains between flares of rosacea and might exhibit severe intermittent flares of acute vasodilation (flushing of rosacea).[6,7] Manifestations at

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CORRESPONDENCE: Stacey Moore, AARS Executive Director, info@aarsmember.org; James Q. Del Rosso, DO, FAOCD, FAAD; Email: jqdelrosso@yahoo.com

various time points in a single patient might differ depending on whether the rosacea is flared or quiescent, the age of the patient, the duration of his or her disease, the frequency and magnitude of rosacea flares, and associated symptomatology.[6,8,9]

Previous consensus articles on rosacea from the American Acne & Rosacea Society (AARS) focused on pathophysiology, clinical assessment based on phenotypic expressions of rosacea, management guidelines, discussions of individual medical therapies, and reviews of physical modalities.[6,10–13] Pathophysiologic mechanisms believed to be operative in rosacea have been covered extensively in the literature.[14–16] The goal of this article is to update the previously published consensus recommendations from the AARS on the management of rosacea, including a review of therapeutic agents and formulations that have become available since the previous publications and a discussion of newer information on physical modalities.

The hope is that the current management recommendations, based on currently available evidence and clinical experience, can serve as a guide to clinicians. In all of the studies referenced in this article, unless otherwise specified, recognized inclusion criteria, exclusion criteria, washout periods of any previous relevant therapies, and tolerability/safety assessments were incorporated and accepted methods for endpoint evaluations were used (e.g., Investigator Global Assessment [IGA], lesion counts, tolerability/safety assessments).

ROSACEA MANAGEMENT RECOMMENDATIONS

Topical ivermectin. Ivermectin (IVM) is an avermectin derivative that has been used extensively for many years in human and veterinary medicine due to its antiparasitic activity and anti-inflammatory properties.[17] The favorable safety profiles of both oral and topical IVM have been correlated with its inability to cross the human blood-brain barrier (BBB) while exhibiting a high affinity for invertebrate neuronal ion channels, allowing for its selective activity against many parasitic organisms.[17] With regard to rosacea, especially in the presence of PP lesions, the anti-inflammatory properties of IVM that appear to correlate with rosacea pathophysiology are of specific investigative interest. The reduction of *Demodex* mite proliferation, which appears to have a role as a trigger factor in a subgroup of patients with rosacea, is another targeted area of research.[18–20]

IVM and rosacea pathophysiology. Avermectin derivatives, including IVM, have been associated with anti-inflammatory effects in multiple *in-vitro* studies; however, the correlation of these effects with rosacea is unknown.[17,21,22] Recently, a single-center, single-treatment pilot study assessed once-daily application of IVM 1% cream on the facial skin of 20 subjects with papulopustular rosacea (PPR). Over a 12-week treatment period, investigators observed marked clinical improvement through dual mechanisms of action.[23] In addition to assessing standard clinical parameters, this study utilized real-time polymerase chain reaction (RT-PCR) and immunofluorescence staining to evaluate multiple inflammatory/immune tissue biomarkers; the study also evaluated *Demodex* mite density via skin surface biopsies. Gene expression levels for multiple biomarkers (e.g., LL-37 [cathelicidin], interleukin [IL]-8, toll-like receptor [TLR]-4, human beta-defensin [HBD]-3) were significantly downregulated following 12 weeks of topical IVM use ($p<0.05$); mean mite density also was significantly reduced ($p<0.001$). All 20 subjects were reported to improve clinically, with 80 percent (16/20) achieving "clear" or "almost clear" results according to Investigator's Global Assessment (IGA) score.[23]

Topical IVM clinical studies. Once-daily IVM 1% cream (Soolantra® Cream, 1%; Galderma Laboratories LP, Fort Worth, Texas) was shown to be significantly more effective than vehicle (n=461) in two pivotal, Phase III, 12-week, double-blind, randomized, controlled trials of adults (N=910) with moderate-to-severe PPR ($p<0.001$).[24] In a 16-week, investigator-blinded, randomized, controlled trial of adults with moderate-to-severe PPR, IVM once daily (N=478) demonstrated significant superiority in efficacy compared to metronidazole 0.75% cream applied twice daily (n=484) ($p<0.001$).[25] An extension assessment of the 16-week study evaluated time to rosacea relapse and maintenance of remission over 36 weeks.[26] In this extension study, IVM cream once daily (n=399) was compared to metronidazole 0.75% cream twice daily (n=365). Both agents were used intermittently for flares in their respective study groups until subjects achieved an IGA score of "clear" or "almost clear"; if new flares occurred, these treatments were restarted until PPR was controlled again, as described above. Median time to first relapse was significantly longer in the IVM group (115 days) than in the metronidazole group (85 days) ($p=0.0365$; Kaplan-Meier plot analysis), and median days free of treatment was higher with IVM use compared to metronidazole use (196 days vs. 169.5 days; $p=0.026$).[26]

Favorable tolerability and safety profiles of IVM 1% cream have also been established in a long-term (52-week) safety study, with low reported rates of cutaneous tolerability reactions (<2% overall), comparable skin tolerability rates to those of metronidazole 0.75% cream and vehicle, and no observed systemic safety signals.[27]

Clinical application of topical ivermectin in rosacea. IVM 1% cream has been shown to be an effective, well-tolerated, and safe treatment for PPR in adults in several randomized, controlled trials of subjects with moderate-to-severe disease and in a case series (N=34) from clinical practice.[24–29] A systematic meta-analysis of 19 randomized, clinical trials reported that IVM 1% cream once daily appears to be more effective than, and at least as tolerable/safe as, other available topical agents used to treat PPR;[30] however, no true head-to-head comparative studies currently exist, with the exception of studies comparing IVM 1% cream to metronidazole 0.75% cream.[30] Based on a review of four randomized, controlled trials (N=1,366) comparing IVM 1% cream to metronidazole 0.75% cream, achieving a study endpoint of "clear" based on IGA assessment optimized remission of rosacea; the median time to relapse was greater than eight months in subjects achieving an IGA rating of "clear," compared with three months for those rated as "almost clear" ($p<0.0001$).[31]

Available data support the use of IVM 1% cream as an option for treatment of PPR as a monotherapy, as well as in combination with a topical alpha$_1$-agonist for treatment of the persistent nontransient facial erythema component of PPR.[28,32–33]

Topical oxymetazoline. Oxymetazoline 1% cream, applied once daily, is a topical alpha$_1$-agonist that was approved by the United States Food and Drug Administration (FDA) for the treatment of persistent facial erythema of rosacea in adults.[34] Morning application is recommended to allow for reduction of the

facial erythema during the day; a noticeable onset of effect generally occurs within 1 to 3 hours after application, with a duration of effect usually observed over 8 to 10 hours. In a Phase II, four-week, double-blind, randomized, controlled trial of adult subjects with moderate-to-severe persistent facial erythema due to rosacea (N=356), oxymetazoline HCl cream (Rhofade® Cream, 1%; Aclaris Therapeutics, Inc., Wayne, Pennsylvania) demonstrated optimal dosing at one percent, compared to 0.5-percent and 1.5-percent concentrations, when applied once or twice daily; safety and application-site skin tolerability were considered favorable and were similar among all study groups.[35]

Topical oxymetazoline clinical studies. Two Phase III, four-week, double-blind, randomized, controlled trials compared oxymetazoline 1% cream to vehicle, both applied once daily, in adult subjects with moderate-to-severe persistent facial erythema due to rosacea at baseline (N=885; 1:1).[36,37] In both pivotal studies, oxymetazoline 1% cream demonstrated significant superiority to vehicle in reaching the primary study endpoint—achieving at least a two-grade reduction in erythema—which was rated separately by investigator and patient at the end of the study ($p<0.001$ in both studies). Digital image analysis evaluating erythema reduction also favored once-daily application of oxymetazoline 1% cream over once-daily application of vehicle ($p<0.001$).[36]

A long-term (52 weeks), open-label study evaluated the use of oxymetazoline 1% cream once daily for moderate-to-severe persistent facial erythema of rosacea in adults (N=440).[38] Overall, this study demonstrated sustained efficacy, tolerability, and safety over the 52 week duration of the study. Discontinuation of treatment, due mostly to application-site adverse events (AEs), occurred in 3.2 percent of subjects, with no systemic safety signals demonstrated; no clinically relevant changes in skin blanching (i.e., over-whitening), inflammatory (PP) lesions, or telangiectasias were noted.[38]

The FDA-approved protocol designs used in the pivotal randomized, controlled trials evaluating both brimonidine 0.33% gel and oxymetazoline 1% cream were very similar.[39,40] However, the studies evaluating oxymetazoline 1% cream included additional follow-up steps to assess worsening of facial erythema, such as rebound after discontinuation.[37–39] Data from the clinical studies and the approved package insert for oxymetazoline 1% cream did not report post-treatment rebound or worsening of facial erythema of rosacea.[34,36–39] AEs reported during treatment phases showed that application-site erythema occurred in one percent of subjects treated with oxymetazoline 1% cream compared to 0.4 percent in vehicle-treated subjects in the pivotal randomized, controlled trials and in two percent of oxymetazoline 1% cream-treated subjects in the long-term study.[34,36–39] These data support that treatment-related worsening of facial erythema (defined as rebound in pivotal clinical studies) noted during active use and/or after discontinuation of once-daily oxymetazoline 1% cream is uncommon.

Clinical application of topical oxymetazoline in rosacea. Oxymetazoline 1% cream may be used for the management of persistent, nontransient, facial erythema of rosacea in adults who present with or without PP lesions.[36–38] In patients with PPR, oxymetazoline 1% cream has been successfully utilized for the reduction of persistent facial erythema along with concurrent use of an agent that reduces PP lesions and perilesional erythema (e.g., topical metronidazole, topical azelaic acid, topical IVM, oral doxycycline).[38]

Topical azelaic acid (AzA). AzA 15% gel (Finacea® Gel, 15%; LEO Pharma Inc., Madison, New Jersey), applied twice daily, is a well-established treatment for PPR.[10,42–45] AzA has been used as a monotherapy, primarily in cases of mild-to-moderate severity, or in combination with oral doxycycline (including sub-antibiotic dose doxycycline) in patients with severe PPR.[44,46] More recently, twice-daily AzA 15% foam (Finacea® Foam, 15%; LEO Pharma Inc., Madison, New Jersey) was approved by the FDA for the treatment PPR in adults, with studies reporting efficacy and safety similar to that observed in the twice-daily AzA 15% gel studies.[47–49] The foam vehicle is a lipid-rich, hydrophilic oil-in-water emulsion.[47,50]

Phase III, 12-week, randomized, controlled trials compared AzA 15% gel and AzA 15% foam, both applied twice daily, to their respective vehicles in adult subjects with facial PPR.[42,48–50] Baseline demographics and disease-related characteristics (i.e., lesion counts, IGAs) were similar in these studies. In the Phase III studies evaluating AzA 15% foam (n=484), application site pain (e.g., stinging, burning) occurred in 3.5 percent and pruritus in 1.4 percent of AzA-treated subjects, all of whom, based on study protocol, were instructed to use gentle skin care products.[48–50] In the AzA 15% gel Phase III studies, the most commonly reported treatment-related AEs were burning, stinging, and/or tingling (29%) and pruritus (11%), with no recommendations given regarding skin care during these studies.[42] Although there are no comparative head-to-head studies of AzA 15% foam versus AzA 15% gel, these data support the concept that proper skin care is a vital component of rosacea management and that vehicle formulation can play an important role in mitigating application-site AEs.[50]

Combination topical therapy. When treating patients with PPR, an important clinical consideration is how to optimally integrate a topical alpha-agonist, used to treat persistent facial erythema of rosacea, with a topical agent, used to treat PP lesions and perilesional erythema. This question was investigated in a multicenter, 12-week, double-blind, randomized, controlled trial that evaluated subjects with moderate-to-severe PPR characterized by marked persistent facial erythema and PP lesions (N=190).[33] Enrolled subjects were randomized to one of three groups:

- Active group 1—brimonidine 0.33% gel, applied once daily in the morning (AM) and IVM 1% cream, applied once daily in the evening (PM), both for 12 weeks (n=49)
- Active group 2—gel vehicle (once daily AM, Weeks 1–4), brimonidine 0.33% gel (once daily AM, Weeks 1–8), and IVM 1% cream (once daily PM, Weeks 1–12) (n=46)
- Vehicle group— gel vehicle (once daily AM) and cream vehicle (once daily PM) for 12 weeks (n=95).

Over the duration of the study, gentle skin care was controlled with a specific cleanser, moisturizer, and sunscreen provided to all subjects. Significantly superior efficacy based on IGA ratings of "clear" or "almost clear" ratings for the reduction in facial erythema and decrease in PP lesions was greatest in the active groups (combined 55.8%) compared to the vehicle group (36.8%) at Week 12 ($p=0.007$).[33] Treatment success was greater in Active Group 1 (IGA "clear" or "almost clear," 61.2%), which received both active treatments for all 12 weeks,

compared to Active Group 2 (50%), in which use of brimonidine 0.33% gel was delayed until Week 5. Skin tolerability favorable in all study groups.[33]

Clinical relevance of combination therapy data. The reductions in facial erythema and PP lesion counts in this topical combination study[33] supports the results of other studies demonstrating the additive therapeutic benefit of combining alpha-agonist therapy with an agent that reduces PP lesions. The best therapeutic outcome was noted when both topical agents were used throughout the study; however, delaying the use of the topical alpha-agonist for the first four weeks of treatment was still associated with marked clinical improvement by Week 12.[33] In addition to parameters assessed by the investigator (e.g., IGA, lesion counts), study subjects in the active groups also reported greater improvements than those in the vehicle group. Lastly, the use of proper skin care appears to be an integral component of successful rosacea management.

Physical modalities (device therapy). Consensus recommendations from the AARS on use of physical modalities for the treatment of rosacea were reviewed in detail in previous publications.[7,8,10,11,13] An important benefit of device treatment for rosacea is that the therapeutic effects are generally seen over a limited number of treatment sessions, which are in contrast to the need for daily treatment over extended periods of time with topical or oral medication. Once an endpoint of an acceptable therapeutic effect is achieved, the results are typically maintained for a number of years. Concurrent medical therapy is often used to complement device treatments.

Telangiectasias/diffuse facial erythema. Since improvements in telangiectasias and facial erythema of rosacea were reported with use of the pulsed-dye laser (PDL), this laser continues to be an important modality in rosacea treatment.[51] Later generations of PDL have incorporated a different pulse format, which largely eliminated the marked bruising observed after treatment with early PDL devices.

Intense pulsed light (IPL) devices have also been used successfully to treat both the facial erythema and dilated facial vessels associated with rosacea.[52] Studies have demonstrated comparable efficacy between updated PDL and IPL devices.[53,54]

Early studies with long-pulsed 532-nm neodymium-doped yttrium aluminum garnet (Nd:YAG) laser demonstrated efficacy in treating telangiectasia.[55] More recent studies using a more powerful 532-nm laser reported excellent results when treating telangiectasia and diffuse erythema in patients with rosacea, which were comparable to those seen with PDL devices.[56] Importantly, the use of lasers, IPL devices, and PDLs have shown superior results treating telangiectatic vessels compared to results achieved treating diffuse facial erythema of rosacea, although both have shown response.[57]

Electrocautery has been employed for many years at low settings to treat visible dilated blood vessels associated with rosacea. While treatment can be successful when performed carefully using a fine-point tip, there is a risk of nonspecific thermal damage that can produce small linear or punctate scars.[37]

PP lesions. Data on the use of lasers and light devices for the treatment of papules and pustules (PP) of rosacea suggest they can be helpful.[51] However, the study methodology used to collect these data failed to capture PP lesion counts or clinical descriptions of rosacea in a controlled manner. Additional well-designed studies evaluating the use of devices for treatment of PPR are needed.

Combination use of a topical alpha-*agonist and device therapy.* Data are limited on the use of topical alpha-agonist therapy in combination with IPL or specific lasers for the treatment of rosacea. One of the authors of this article (ET), who has extensive experience with the use of devices for rosacea, suggests that the use of a topical alpha-agonist and physical devices are complementary. The natural appearance and the degree of improvement of diffuse facial erythema with use of either topical brimonidine or topical oxymetazoline usually produces a better visible facial appearance than the partial improvement typically seen with devices alone. The partial response achieved when using laser/light devices to treat diffuse facial erythema, combined with the excellent results seen with these devices when treating telangiectasia[51–57] (which are not responsive to the use of a topical alpha-agonist), suggest that a topical alpha-agonist can be initiated after laser and light treatments. There have been some early studies that suggest that the use of an alpha-agonist immediately following treatment with these devices diminishes the pulse treatment erythema that commonly occurs with these devices.[58] Hopefully, further studies will help determine whether use of a topical alpha-agonist will change or compromise the therapeutic effects of the device. Additionally, there are studies in progress that are evaluating the use of alpha-agonists to compliment device treatments when used a few days after treatment, as well as literature supporting the potential inhibition of vascular endothelial growth factor with brimonidine, which suggests a potential additive effect of device treatment followed by the use of a topical alpha-agonist.[59] At this point, we do not have sufficient data regarding the complimentary use of these agents with laser and light devices to make evidence-based treatment recommendations.

Adverse effects associated with the use of an ablative device followed directly by the use of a topical alpha-agonist have been observed.[60] Potentially, a treatment with any device that damages the epidermal barrier can result in increased percutaneous absorption of a topically applied alpha-agonist, increasing the risk of hypotension. Studies exploring the safe and complimentary use of devices and topical alpha-agonist therapy are important and much needed.

Microfocused ultrasound and bipolar radiofrequency. There are a number of devices that cause nonselective vascular damage that hold some promise for success in the treatment of rosacea. Microfocused ultrasound with visualization (MFU-V) and bipolar radiofrequency pins have been shown to improve the diffuse facial erythema associated with rosacea.[61] Data from the study evaluating MFU-V technology in patients with rosacea was generated using the same rigorous parameters as those used in the alpha-agonist pivotal clinical trials, which bolsters the investigators' findings. Moving forward, clinical studies evaluating the efficacy and safety of devices for the treatment of rosacea could generate better quality data by incorporating validated assessment methods, such as the IGA, Clinician's Erythema Assessment, telangiectasia grading score, inflammatory lesion counts, standardized side effect assessments, and patient efficacy evaluations, especially when the number of study participants is limited or a split-faced study design is being utilized.

CONSENSUS RECOMMENDATIONS FOR THE MANAGEMENT OF ROSACEA

The already published guidelines for rosacea management primarily focus on incorporating medical and/or device therapies that are

correlated with the visible manifestations of rosacea.[7,8,10–13,62–66] In all cases, proper skin care, photoprotection, and avoidance of patient-specific rosacea triggers are suggested. How therapies are used, either concurrently or in a staggered fashion, might be considered by some to be more art than science, as clinical studies and outcomes data are currently lacking. However, some combination approaches have been addressed in the literature.[33,46,58] These include the initial use of topical metronidazole or topical azelaic acid concurrently with oral doxycycline for treatment of severe PPR with transition to topical therapy alone after adequate response is achieved; topical brimonidine and topical ivermectin for treatment of PPR with diffuse persistent facial erythema of at least moderate severity; and combination treatment with potassium titanyl phosphate laser and topical brimonidine for diffuse persistent facial erythema of rosacea.[36,46,58] Table 1 depicts consensus recommendations from the AARS on rosacea management correlated with clinical manifestations observed at the time of presentation.[7,8,10–13,62–76]

SUMMARY

This article provides an update to previously published consensus recommendations from the AARS on rosacea management, including discussions of topical ivermectin, topical oxymetazoline, combination therapy approaches, and physical devices. Consistent with what many publications on rosacea currently emphasize, clinicians are encouraged to define the clinical manifestations currently present in each individual patient and to select therapies that correlate with the optimal treatment of those manifestations. There are less data available on how to optimally combine therapies; however, it appears that rationally selected medical therapies can be utilized concurrently. As the pathophysiology of rosacea is multifactorial, the clinical presentation of rosacea is heterogeneous. Rosacea is a chronic and recurrent inflammatory disorder, and clinical manifestations often vary in their nature and severity over time. This might necessitate an adjustment in management. As new data become available, management approaches should be updated.

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TABLE 1. American Acne & Rosacea Society recommendations for rosacea management options*

ROSACEA PRESENTATION	MANAGEMENT OPTIONS	QUALITY OF EVIDENCE OF MANAGEMENT OPTIONS (A, B, C)	EVIDENCE COMMENTS
Persistent central facial erythema without papulopustular (PP) lesions	• Topical alpha-agonist (brimonidine, oxymetazoline) • Intense pulsed light (IPL), potassium titanyl phosphate (KTP) crystal laser, or pulsed-dye laser	B: Systematic review/meta-analysis of lower-quality clinical trials or studies with limitations and inconsistent findings; lower-quality clinical trial	• More data are needed on optimal use of specific device therapies and topical alpha-agonist therapy in combination
Diffuse central facial erythema with PP lesions	• Topical metronidazole • Topical azelaic acid • Topical ivermectin • Oral tetracyclines • Topical alpha-agonists • Oral isotretinoin	B: Systematic review/meta-analysis of lower-quality clinical trials or studies with limitations and inconsistent findings; lower-quality clinical trial	• Combination of an oral and topical agent that reduce PP lesions and perilesional erythema based on severity; topical alpha-agonist used for persistent background erythema caused by fixed dilated vasculature • Subantibiotic dose doxycycline is the preferred initial oral therapy option due to absence of bacterial selection pressure • Oral azithromycin is an alternative option if an oral tetracycline is not effective or poorly tolerated (caution in some patients due to potential cardiac risks) • Oral isotretinoin for refractory disease (transition to intermittent therapy after initial control) • Other alternative topical agents include sulfacetamide-sulfur, calcineurin inhibitors, retinoids, and permethrin (limited data available on these agents)[67,68] • While the data on the use of IPL, KTP or pulsed-dye laser are limited for PP lesions, these options are useful to treat erythema
Flushing of rosacea (acute-subacute intermittent vasodilation)	• Flushing is better prevented than treated via avoidance of known triggers, such as sun exposure and photoprotection • Use of low-dose oral drugs with vasoconstrictive properties, including mirtazapine, propranolol, or carvedilol[69–72] • The use of intradermal botulinum toxin achieved good results in a small group of patients, but there remain limited data[73]	B: Systematic review/meta-analysis of lower-quality clinical trials or studies with limitations and inconsistent findings; lower-quality clinical trial	• Data are limited on the management of flushing of rosacea[69–72] • Limited data exist on topical therapies • Some botanicals and natural ingredients might improve facial redness and flushing (niacinamide, parthenolide-free extract of feverfew (*Tanacetum parthenium)*, licorice derivatives, chamomile, green tea) based on preliminary small studies[74] • An anti-inflammatory cleanser night mask combination was found to markedly reduce facial redness (limited data)[75]
Ocular rosacea	• Lid hygiene, sunglasses, eye lubrication formulations.[68,76,77] • Cyclosporin ophthalmic emulsion (3-month, randomized, controlled trial [n=37])[78] • Topical metronidazole or ivermectin (blepharitis; applied to external eyelid skin)[68,71,76,77,79] • Oral doxycycline, erythromycin, or azithromycin[68,76,80,81]	B: Systematic review/meta-analysis of lower-quality clinical trials or studies with limitations and inconsistent findings; lower-quality clinical trial	• Data are based on clinical experience, case reports, and small studies • Topical corticosteroids for short-term therapy but avoid chronic use[76] • Oral omega-3 fatty acids may reduce inflammation and dry eye symptoms • Subantibiotic dose doxycycline suggested for long-term therapy[76]
Granulomatous rosacea	• Oral tetracyclines[82] • Topical pimecrolimus (case reports)[82] • Oral isotretinoin (0.7mg/kg/day for 6 months)[83] • Oral dapsone[82] • Intense pulsed-dye laser (case)[82] • Photodynamic therapy (case)[82] • Topical brimonidine[84]	C: Consensus guidelines; usual practice, expert opinion, case series—limited trial data	• No current standard of treatment; limited data based mostly on case reports[82] • Oral isotretinoin may produce improvement without recurrence[83]
Phymatous rosacea	• Surgical therapy for fully developed phymatous changed (carbon dioxide laser, erbium-doped yttrium aluminium garnet (YAG) laser, electrosurgery, dermabrasion)[85,86]	C: Consensus guidelines; usual practice, expert opinion, case series—limited trial data	• Treatment selection dependent on stage of development (early or fibrotic) and extent of inflammation (active or burnt out) • Oral isotretinoin might improve early soft phymatous changes due to sebaceous hyperplasia

* Reader directed to read body of paper for more details and also to reference specific evidence; management options not listed in any specific order of preference

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