

Update on the management of rosacea

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Abstract: Refining diagnostic criteria has identified key characteristics differentiating rosacea, a chronic skin disorder, from other common cutaneous inflammatory conditions. The current classification system developed by the National Rosacea Society Expert Committee consists of erythematotelangiectatic, papulopustular, phymatous, and ocular subtypes. Each subtype stands as a unique entity among a spectrum, with characteristic symptoms and physical findings, along with an intricate pathophysiology. The main treatment modalities for rosacea include topical, systemic, laser, and light therapies. Topical brimonidine tartrate gel and calcineurin inhibitors are at the forefront of topical therapies, alone or in combination with traditional therapies such as topical metronidazole or azelaic acid and oral tetracyclines or isotretinoin. Vascular laser and intense pulsed light therapies are beneficial for the erythema and telangiectasia, as well as the symptoms (itching, burning, pain, stinging, swelling) of rosacea. Injectable botulinum toxin, topical ivermectin, and microsecond long-pulsed neodymium-yttrium aluminum garnet laser are emerging therapies that may prove to be extremely beneficial in the future. Once a debilitating disorder, rosacea has become a well known and manageable entity in the setting of numerous emerging therapeutic options. Herein, we describe the treatments currently available and give our opinions regarding emerging and combination therapies.

Keywords: rosacea, vascular laser, rhinophyma, management, guidelines

Introduction and epidemiology

Fascination with rosacea has been historically illustrated in medical art and literature, with imagery found in the Louvre dating back to the 15th century.¹ Through the refinement of diagnostic criteria, several key characteristics differentiating rosacea from common skin findings have been identified, particularly central facial erythema and acneiform papules and pustules. Specific sparing of the perioral and periorcular regions has emerged as an essential criterion for the diagnosis.² In 2002, the National Rosacea Society Expert Committee developed a classification system for rosacea in order to standardize subtypes and variants that has since been widely accepted and continues to aid in research and epidemiological studies.³ The committee defined four subtypes based on clinical characteristics: subtype I, or erythematotelangiectatic rosacea (ETR), defined by flushing and persistent central facial erythema (Figure 1); subtype II, or papulopustular rosacea (PPR), consistent with constant erythema and transient pustules and papules in the central facial distribution (Figure 2); subtype III, or phymatous rosacea, characterized by thickened skin with irregular contours overlying the ears, cheeks, chin (gnathophyma), forehead (metophyma), and nose (rhinophyma) (Figure 3); and subtype IV, or ocular rosacea, represented by a watery, burning, dry,

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Figure 1 Erythematotelangiectatic rosacea.

Note: Central facial erythema (most prominently on the cheeks) with telangiectasias.

itchy, and light sensitive ocular sensation with a bloodshot appearance. An associated cutaneous rosacea may or may not be present (Figure 4). However, a wide range of overlapping symptoms makes coinciding subtypes a clinical reality.

The prevalence of rosacea in recent years ranges from 1% to 22% depending on the methodology and population sample analyzed.⁴⁻⁶ Reports from general population surveys assess higher sample numbers and may be more reflective of overall prevalence, whereas reports from dermatology clinics represent a more select population and yield smaller prevalence ranges. More recently, large retrospective database studies have yielded prevalence rates ranging from 1.3% to 2.1%.⁷⁻¹² Such low rates may be misrepresentative since the administrative databases only recorded patients with severe rosacea symptoms, potentially missing a significant percentage of patients with mild disease.

Generally, women are more often affected than men. Subtype I (ETR) is found to be most prevalent, followed by subtype II (PPR), and rhinophyma is seen mostly in men over



Figure 2 Papulopustular rosacea.

Note: Multiple papules and pustules on the central face, lacking comedones and sparing the perioral area.

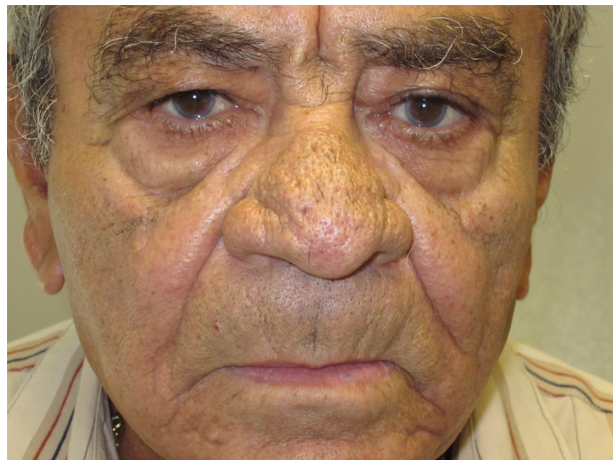


Figure 3 Phymatous rosacea.

Note: Thickened, glandular skin of the nose, creating a cosmetic deformity.

40 years of age.¹³ Ocular rosacea is difficult to diagnose due to wide diagnostic criteria; consequently, incidence rates range from 6% to 72%, with the greatest prevalence reported from ophthalmology clinics. Unlike facial rosacea, ocular rosacea affects both sexes equally.¹⁴ The prevalence rates are highly dependent on the classification system, cohort selection, and methodology of collection. Considering these limitations, rosacea as a dermatological entity might be more common than previously suspected.

Natural history and pathophysiological mechanisms underlying rosacea

Despite the depth of current research, the pathophysiology of rosacea remains primarily theoretical and requires further investigation. There is continued debate between rosacea



Figure 4 Ocular rosacea.

Note: Erythematous conjunctiva with increased watery discharge in the setting of acutely flared granulomatous rosacea.

variants representing distinct phenotypes or different stages within one pathological progression. Histologically, dilated lymphatics and blood vessels, as well as perivascular infiltration of CD4⁺ helper T-cells, macrophages, and mast cells can be readily seen.¹⁵ In healthy skin, activation of keratinocyte toll-like receptors (TLRs) by pathogenic cell wall fragments stimulates the cells to coordinate an appropriate defense response, releasing antimicrobial peptides (AMPs) such as cathelicidins and defensins. Originally synthesized as propeptides, these AMPs remain inactive until cleaved by proteases into active fragments. In rosacea, genetic predisposition may precipitate an inappropriate response to different environmental stimuli via TLRs including extremes of temperature, abnormal microbial skin colonization, and ultraviolet light exposure.

The first identified human cathelicidin AMP, LL-37, is released by keratinocytes and cleaved by skin serine proteases (kallikrein 5) into its immunogenic antimicrobial form. Specifically, vitamin D activation by ultraviolet light exposure and endoplasmic reticulum stressors sensed by TLRs on keratinocytes have been shown to induce increased expression of cathelicidin LL-37, triggering molecular cascades ultimately resulting in erythema.¹⁶ This partially explains why the face, a highly sun-exposed area, is the main site affected in rosacea.¹⁷ LL-37 has been extensively involved in describing the pathogenic inflammatory response, impaired antimicrobial activity, and vascular dysfunction of rosacea.

Another trigger for cutaneous protease activation of cathelicidins is upregulation of TLR-2 in keratinocytes by *Demodex folliculorum*, a species of commensal saprophytic mite that colonizes pilosebaceous follicles of the skin. *D. folliculorum* releases an antigen that sensitizes TLR-2 on keratinocytes to induce the pathway of inflammation associated with protease activation of AMPs, including LL-37.^{18,19} Other microbial agents reportedly associated with rosacea are *Bacillus oleronius*, *Staphylococcus epidermidis*, *Helicobacter pylori*, and *Chlamydomphila pneumoniae*. The exact mechanisms implicating the aforementioned microorganisms in ERT and PPR are yet to be identified or substantiated.²⁰

In addition to erythema, neurocutaneous symptoms, including pain, burning, and stinging, have also been reported in rosacea. Activation of peripheral sensory nerve endings like transient receptor potential channels by heat, cold, alcohol, spicy foods, and exercise releases vasoactive neuropeptides that contribute to neurogenic inflammation.²¹ As a result, not only do the blood vessels adapt and become hyperpermeable, allowing for increased blood flow and influx of inflammatory cells, but lymphatic vessels also expand to contribute

to characteristic flushing, erythema, and edema. Dilation of precapillary arterioles and post-capillary venules allow protein leakage and leukocyte recruitment via upregulation of selectins and cell adhesion molecules.¹⁶ Future research will help to clarify the exact pathophysiological mechanisms involved in rosacea. Currently, it is clear that the innate immune and the sensory and autonomic nervous systems are overstimulated with dysregulated interactions, leading to a chronic pathological inflammatory state. Defining the precise molecular interactions and the importance of genetic predisposing factors are puzzle pieces that remain to be solved.

Current and emerging treatments: topical, systemic, laser, and light therapies

No single treatment is completely curative for rosacea. Fortunately, many treatments have been studied and can give relief when used in the right clinical scenario (Table 1). Pharmacological agents, when used in combination with medical devices, show better results than either treatment alone and can provide improvements never thought possible in the past (Figure 5). Since rosacea is a chronic inflammatory condition that waxes and wanes, with many triggers, the goal of treatment should be to subside acute flares with rapid-acting treatments and maintain the results with lifestyle modification and prolonged combination therapy. The avoidance of triggers, particularly ultraviolet light exposure, is critical for long-term improvement and disease control, and should be an essential component of patient education when prescribing at-home skin care and lifestyle adjustments.

Topical therapies

Brimonidine tartrate gel (Mirvaso[®], Galderma Laboratories, Fort Worth, TX, USA), an α -2 adrenergic receptor agonist, is the only approved topical treatment for the persistent facial redness of rosacea and works by reversing skin vasodilation. In a recent year-long study, brimonidine tartrate gel 0.5% applied once daily proved to be both efficacious and safe, regardless of the presence of concomitant therapies.²² The clinician's erythema assessment, patient's self-assessment, telangiectasia grading assessment, and inflammatory lesion count were utilized to quantify disease severity.²³ Three hours following application, the clinician's erythema assessment and patient's self-assessment were reassessed and found to be significantly improved, an effect that was maintained throughout the study. Supporting this result, Jackson et al showed improvement in facial erythema within 30 minutes of initial daily application of brimonidine tartrate in Phase III

Table 1 Rosacea subtypes and corresponding topical, oral, and alternative treatments

Treatment	Ocular	Phymatous	PPR	ETR
Topical ³⁰				
FDA-approved	–	–	Metronidazole 0.75%, 1% ^{27,28,33–35,61} Azelaic acid 15% ^{27,28,60} Sodium sulfacetamide 10% + sulfur 5% ²⁹ Ivermectin 1% cream ^{36–38}	Brimotidine tartrate gel 0.5% ^{22–24} Oxymetazoline solution 0.05% ²⁵
Non FDA-approved	Azithromycin ⁵⁹	–	BP-clindamycin ⁴¹ Encapsulated BP gel ⁴² Tacrolimus ointment ⁶⁴ Pimecrolimus 1% cream ^{31–33} Permethrin 5% cream ^{34–36,38}	BP-clindamycin ⁴¹ Encapsulated BP gel ⁴² Tacrolimus ⁶⁴ Pimecrolimus 1% cream ^{31–33} Permethrin 5% cream ^{34–36,38}
Oral ⁵¹	Doxycycline ^{57,58} Isotretinoin ⁶⁶ Ivermectin ⁴⁰ Tetracyclines ⁵¹ Macrolides ⁵¹	–	Isotretinoin ^{66,67–69} Ivermectin ³⁷ Doxycycline ^{48,52,54,55,60,61,67} Tetracyclines ^{13,43} Macrolides ^{62,63,64} Metronidazole ⁶⁵ Oral zinc ^{76,77}	Isotretinoin ^{66,67–69}
Alternative	Lid hygiene	Nd:YAG laser ^{122,123} Er:YAG laser ^{136–139} CO ₂ laser ^{124–134,137,138} PDL ¹³¹ Surgical (blade and radio) excision ^{121,136} Cryosurgery Dermabrasion	Novel lotion (caffeine, zinc gluconate, bisabolol, <i>Eperua falcata</i> bark extract, and palmitoyl tripeptide-8) ⁴⁴ <i>Quassia amara</i> 4% gel ⁴⁵ Hyaluronic acid 0.2% cream ⁴⁷ OnabotulinumtoxinA ^{151,152} Other natural Ingredients (botanicals and anti-inflammatories) ⁴³	Hyaluronic acid 0.2% cream ⁴⁷ Argon laser ⁸³ PDL ^{78,85,87–97,107,117,120,149,150} IPL ^{98–111} KTP laser ^{113–117} Nd:YAG laser ¹²⁵ OnabotulinumtoxinA ^{151,152}

Abbreviations: BP, benzoyl peroxide; ETR, erythematotelangiectatic rosacea; PPR, papulopustular rosacea; Nd:YAG, neodymium:yttrium-aluminum-garnet laser; Er:YAG, erbium:yttrium-aluminum-garnet; PDL, pulsed dye laser; IPL, intense pulsed light; KTP, potassium titanyl phosphate; FDA, US Food and Drug Administration.

clinical studies.²⁴ Oxymetazoline, a potent α -1 and partial α -2 receptor agonist, is another efficacious agent for reducing facial erythema, with data primarily limited to case reports, and is now in clinical development for the treatment of ETR. In two adults with refractory erythema and flushing associated with rosacea, oxymetazoline nasal solution 0.05% applied to facial skin demonstrated significant decreased erythema one hour after application that progressed to dra-

matic improvement within 3 hours and remained throughout the day²⁵ (Figure 6).

Some of the more commonly used US Food and Drug Administration (FDA)-approved topical agents for PPR are metronidazole and azelaic acid, both of which are available in a variety of strengths and formulations. The efficacy, safety, and cost-effectiveness of both agents are well demonstrated in a number of well controlled randomized studies.²⁶ A few

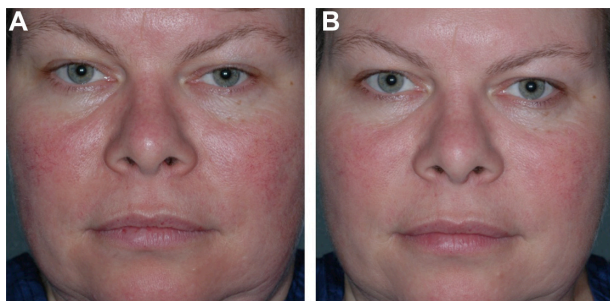


Figure 5 Before (A) and after (B) injectable botulinum toxin (Botox®, 10 U, 0.05 mL aliquots every 1–2 cm) intradermally into each cheek in combination with pulsed dye laser (10 mm, 10 msec, 7 J/cm).

Note: Clinical results and symptomatic relief were seen rapidly after the treatments.

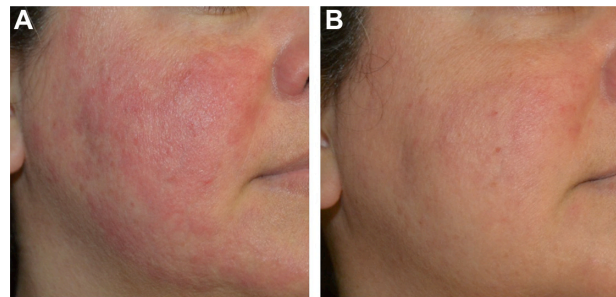


Figure 6 Before (A) and after (B) oxymetazoline (Afrin®) combined with a topical moisturizing cream (CeraVe®) applied twice daily. Significant improvement in facial erythema was seen after only one day of application.

studies show comparable efficacy of metronidazole and azelaic acid, with one study of azelaic acid gel 15% twice daily yielding a superior reduction in facial erythema versus metronidazole gel 0.75% twice daily after 8 weeks of use.^{27,28} Long available sodium sulfacetamide 10% + sulfur 5% cleansers and leave-on formulations have also proven to be efficacious for the treatment of inflammatory lesions and facial erythema based on small studies; however, they are not used as frequently, perhaps due to their malodorous sulfur content, irritant potential, and limited published data.²⁹ The mechanisms of action for these topical agents are unknown and the decision to utilize monotherapy or combination regimens depends on the severity of PPR.

There are a number of alternative topical non-FDA-approved therapies for patients with rosacea that is refractory to primary topical treatments. These agents include topical calcineurin inhibitors such as tacrolimus and pimecrolimus, macrolides such as erythromycin, clindamycin, and azithromycin, and others such as retinoids, permethrin, benzoyl peroxide (BP), and BP-clindamycin. Their therapeutic benefits are widely recognized despite the limited evidence in the small number of clinical studies.³⁰ Pimecrolimus cream 1% has been used to treat both PPR and ETR with mixed results, but worthy of a trial in unmanageable cases.^{31,32} In an open-label randomized study of 49 patients, pimecrolimus 1% cream was as effective as metronidazole 1% cream.³³ The senior author (JE) has found considerable benefit in using topical pimecrolimus in combination with oral treatments and/or vascular laser therapy for both ETR and PPR types, and this is his “go-to” therapy for patients with refractory or flared moderate to severe presentations.

Macrolides, such as erythromycin and its analogs, clindamycin and azithromycin, have limited data with regard to reduction of inflammatory lesions and are not recommended as treatments of choice due to potential induction of antibiotic-resistant bacterial strains.³⁰ However, many practicing physicians continue to use these treatments as first-line because they believe them to have intrinsic anti-inflammatory properties that not only improve facial erythema and papules but also the associated symptoms of rosacea.

The antiparasitic properties of permethrin showed efficacy in one study of 63 subjects comparing permethrin cream, topical metronidazole, and placebo.³⁴ Patients were randomly divided into three treatment groups and received either permethrin 5% cream (n=23), metronidazole (n=20), or placebo cream (n=20) for up to 2 months of treatment twice daily. Outcomes of erythema, numbers of papules/pustules/nodules, and *D. folliculorum* colonization were assessed at baseline

and every 15 days. *D. folliculorum* colonization was reduced by both agents; however, permethrin 5% had a greater effect than metronidazole. Both active treatments reduced erythema and papules, but had no effect on pustules or telangiectasia. Overall, permethrin 5% was found to be a new and powerful tool against dense colonization of *D. folliculorum*, a proposed key player in the pathogenesis of rosacea.

These results clarify previous equivocal findings of permethrin 5% cream and metronidazole 0.75% gel in a pilot study of six patients who used each therapy on half of the face for up to 10 weeks twice daily.³⁵ More recently, a case study of an immunocompetent patient with refractory rosacea secondary to *Demodex* dermatitis demonstrated symptom resolution with oral ivermectin and permethrin 5% cream.³⁶

A novel topical agent, ivermectin 1% cream, recently approved by the FDA, was studied in the treatment of PPR in two randomized, double-blind, vehicle-controlled Phase III studies of identical design conducted in the USA (n=683) and Canada (n=688).³⁷ Stein et al compared once-daily ivermectin 1% cream with vehicle for a duration of 12 weeks utilizing the investigator global assessment of disease and inflammatory lesion counts as efficacy parameters. A statistically significant percentage of patients at both trial sites treated with ivermectin 1% compared with vehicle achieved success according to the investigator global assessment, defined as “clear” or “almost clear” skin at week 12. There was also a significantly greater percent reduction in inflammatory lesion counts in the treatment group when compared with control. Adverse events were assessed throughout and were found to be more frequent in the patients treated with vehicle only. The most common complaints were skin burning, pruritus, and dry skin, with no serious adverse events reported. The results of these two 12-week studies identified ivermectin 1% cream as unequivocally potent and safe in treating inflammatory lesions in PPR patients.

Developed from the naturally occurring antiparasitic compound avermectin, ivermectin has both anti-inflammatory and antiparasitic properties that have been utilized orally in the treatment of rosacea-like demodicidosis with topical promethazine and as monotherapy topically for head lice and orally for chronic blepharitis secondary to *Demodex*.³⁸⁻⁴⁰ Selective binding of ivermectin to glutamate-gated chloride channels in invertebrates has been shown to reduce *Demodex* colonization in both demodicidosis and blepharitis. Ivermectin induces anti-inflammatory effects via nuclear factor- κ B pathway inhibition and subsequently decreases the release of inflammatory cytokines. Given that none of the classic rosacea therapies address both the inflammatory and infectious pathogenesis

of the disorder, innovative use of ivermectin may prove to be beneficial in the future and warrants further investigation.

Benzoyl peroxide and antibiotic combinations, eg, BP-erythromycin and BP-clindamycin, have long been used for reduction of papulopustular lesions. In a randomized, double-blind, vehicle-controlled trial of BP-clindamycin gel, daily application demonstrated efficacy in 26 patients with moderate to severe rosacea.⁴¹ The percentage change in number of papules and pustules from beginning to end of the 12 weeks was reduced by a mean 71.3% in the treatment group compared with 19.3% in the vehicle only group, with a statistically significant difference between the two results. Side effects of itching, burning, and bleaching of hair and clothing were reported in eleven patients. Consequentially, a recent randomized, dose-ranging Phase II study of 1% and 5% BP-encapsulated in silica microcapsules proved to be both highly effective and well tolerated in PPR patients, as the encapsulation added protection for the epidermis from the irritant effects of BP.⁴²

Natural cosmeceutical options serve as an additional branch of the market available to rosacea patients. Natural ingredients reported in the literature that provide hydrating, anti-inflammatory, and antioxidant properties capable of calming the inflammatory manifestations of rosacea include colloidal oatmeal, niacinamide, feverfew, licorice, teas, coffeeberry, aloe vera, chamomile, turmeric, and mushroom extracts.⁴³ Further, a novel topical lotion (Redness Neutralizer[®], SkinCeuticals, New York, NY, USA) containing caffeine, zinc gluconate, bisabolol, *Eperua falcata* bark extract, and palmitoyl tripeptide-8, was used twice daily in a group of 25 patients with PPR who had been previously treated successfully with topical or oral therapy, but were unsatisfied with the remaining background erythema.⁴⁴ All efficacy categories demonstrated statistically significant improvement between baseline and follow-up at weeks 4 and 8. Although one patient developed burning and increased erythema and withdrew from the study, the remaining 24 patients found the treatment very tolerable without clinical signs of irritation. Overall, 95% of patients were satisfied with the products and the results after 8 weeks of twice-daily use.

In another single-center, open-label study, a group of 30 patients with rosacea of variable severity were treated with 4% *Quassia amara* extract topical gel for 6 weeks. Reportedly, *Q. amara* possesses antiparasitic and anti-inflammatory properties that have the capability to decrease the inflammatory response with few complications.⁴⁵ Efficacy comparable with that of first-line topical treatments like azelaic acid and metronidazole was observed after *Q. amara*

treatment, with superb tolerability. Finally, a formulation of low molecular weight hyaluronic acid sodium salt 0.2% cream (Bionect[®] Cream, Innocutis Holdings, Charleston, SC, USA) applied twice daily for 8 weeks showed a statistically significant reduction in papules, erythema, burning, stinging, and dryness in a small study.⁴⁶ Along with excellent tolerability, a reduction in papules, erythema, burning/stinging, and dryness was clearly apparent by week 4 and remained by the final visit at week 8. Notably, erythema was reduced by the greatest amount, with an approximate 50% improvement by week 2. This study demonstrates the importance of skin barrier maintenance and repair in the pathogenesis of rosacea. With a hydrophilic structure, low molecular weight hyaluronic acid penetrates the stratum corneum where it interacts with fibrin and collagen to support remodeling of the extracellular matrix. This mechanism, along with induction of the antimicrobial peptide β -defensin 2 release from keratinocytes, ultimately accelerates re-epithelialization and reduces pain and edema.⁴⁷

Systemic therapies

Modified-release doxycycline 40 mg once daily (Oracea[®], Galderma Laboratories) is the only systemic agent that is approved by the FDA for the treatment of PPR and provides anti-inflammatory effects with subantimicrobial dosing. The formulation allows for immediate release of 30 mg with delayed release of 10 mg once ingested.⁴⁸ Through inhibition of numerous matrix metalloproteinases, a reduction in the quantity and activity of serine protease kallikrein 5 results in decreased production of cathelicidin LL-37, the same AMP that has been highlighted in the pathogenesis of rosacea.⁴⁹ Key anti-inflammatory actions of doxycycline in rosacea include: downregulation of cytokines, reducing neutrophil infiltration, inhibition of nitric oxide and its vasodilatory effects, reduction of reactive oxygen species, slowing connective tissue destruction, and inhibition of matrix metalloproteinases.⁵⁰

Several studies have shown the effectiveness of doxycycline at subantimicrobial doses in the treatment of PPR, both as monotherapy and in conjunction with topical agents.⁵¹ In a pivotal randomized, dose-ranging, double-blind trial, similar therapeutic effects were seen in patients with PPR using metronidazole 1% gel and either 40 mg or 100 mg delayed-release doxycycline over 16 weeks.⁵² Notably, no statistically significant difference was seen between the two treatment groups in any outcome measures; however, adverse events, including nausea, vomiting, diarrhea, and abdominal pain, occurred solely in those treated with doxycycline

at an antibiotic dose. Subsequently, a large-scale study demonstrated excellent results in 826 patients with mild to moderately severe rosacea taking daily doxycycline 40 mg monotherapy (30 mg immediate-release and 10 mg delayed-release beads).^{53,54} Nearly 75% of participants achieved clear or near clear results on the five-point investigator global assessment scale.

Combination therapy has demonstrated more substantial improvements than monotherapy. Oral doxycycline as well as minocycline with azelaic acid or metronidazole has shown substantial improvements in inflammatory lesion counts in multiple studies.^{55–65}

Alternative systemic therapies for PPR and ocular rosacea, which are not FDA-approved, include tetracycline derivatives (doxycycline and minocycline at antimicrobial doses), macrolides (erythromycin, azithromycin, and clarithromycin), metronidazole, and oral isotretinoin. There are several considerations when using systemic treatments, including allergic reactions, drug rash with eosinophilia and systemic symptoms (DRESS syndrome), cutaneous hyperpigmentation, benign intracranial hypertension, autoimmune hepatitis, and drug-induced lupus-like syndrome. More common concerns, and ones to discuss with patients at treatment onset, include gastrointestinal intolerance (antibiotics), metallic taste (macrolides > metronidazole), drug interactions, and photosensitivity (doxycycline > minocycline). Tetracyclines should be avoided in pregnant or lactating women and in children with developing teeth because they can result in permanent staining (dark yellow-gray teeth with a darker horizontal band across the top and bottom rows of teeth), and may also affect bone and tooth growth.

When patients cannot tolerate tetracyclines due to photosensitivity or gastrointestinal adverse effects, such as pill esophagitis, azithromycin has been suggested as an alternative oral treatment option.⁶² In one case report, a 52-year-old patient with rosacea was successfully treated with azithromycin 500 mg daily after failing numerous regimens, including topical BP, topical metronidazole twice daily, oral metronidazole 500 mg for 2 weeks, oral isotretinoin 10 mg for one month, and oral doxycycline 200 mg for one month.⁶³ With dramatic improvement noticed after 2 weeks of treatment, the patient's lesions had almost completely disappeared by week 10, with no medication-induced side effects. Another case study in a post-menopausal woman of the same age (52 years) with progressive rosacea symptoms and ocular involvement showed gradual erythema and papulopustule improvement while using combination therapy with tacrolimus 0.1% ointment for 30 days in addition

to azithromycin 1,000 mg daily for 45 days, then 500 mg daily for an additional 45 days.⁶⁴ Historical data show that oral metronidazole 200 mg taken twice daily for 6 weeks resulted in marked improvement in papular and pustular lesions; however, its link to potential side effects such as neuropathy, seizures, and a disulfiram-like reaction have limited further research.⁶⁵

Oral isotretinoin is typically reserved for severe cases of all rosacea subtypes. This retinoid derivative of vitamin A not only reduces the size of sebaceous glands and subsequently sebum production, but also possesses anti-inflammatory, immunomodulatory, and antineoplastic properties.⁶⁶ For acne, it is commonly given for a duration of 6 months in daily doses ranging from 0.2 mg/kg to 1.0 mg/kg.¹³ Participation in the iPledge program, which is mandated by the FDA in order to minimize the risk of teratogenicity from pregnancy while on therapy, as well as numerous drug-induced side effects, such as mucosal dryness, retinoid dermatitis, photosensitivity, and increased blood triglycerides and liver function tests, make prescribing more tedious.

In a large dose-finding, randomized, double-blind trial comparing the use of different systemic isotretinoin dosages with both doxycycline and placebo, the ultimate effective dose of isotretinoin was found to be 0.3 mg/kg for a minimum duration of 3 months.⁶⁷ Patients with subtypes II (papulopustular) and/or III (phymatous) rosacea were randomly assigned into one of five treatment groups: doxycycline 100 mg daily for 14 days then 50 mg daily (n=143), isotretinoin 0.1 mg/kg (n=109), 0.3 mg/kg (n=142), or 0.5 mg/kg (n=109), or placebo (n=46). These groups were followed until the interim analysis, at which point isotretinoin 0.3 mg/kg stood out as the most efficacious and tolerable dosage. The two other isotretinoin dosage arms were closed, leaving doxycycline and isotretinoin 0.3 mg/kg for the final analysis after 12 weeks of treatment. Overall, isotretinoin 0.3 mg/kg showed statistically significant noninferiority when compared with doxycycline therapy, with investigators documenting complete remission in 24% of patients treated with isotretinoin 0.3 mg/kg compared with 13.6% of patients treated with doxycycline. Notably, more patients in the isotretinoin group reported adverse drug reactions (33%) compared with the doxycycline group (25%); however, these differences did not reach statistical significance. For recalcitrant rosacea with problematic relapses, continuous "microdose" isotretinoin (0.04–0.11 mg/kg daily) in patients without a risk of teratogenesis has shown promise.^{68,69}

For the senior author (JE), oral isotretinoin has been particularly useful in the PPR and phymatous subtypes (Figure 7). When multiple subtypes coexist in patients with rosacea, it is

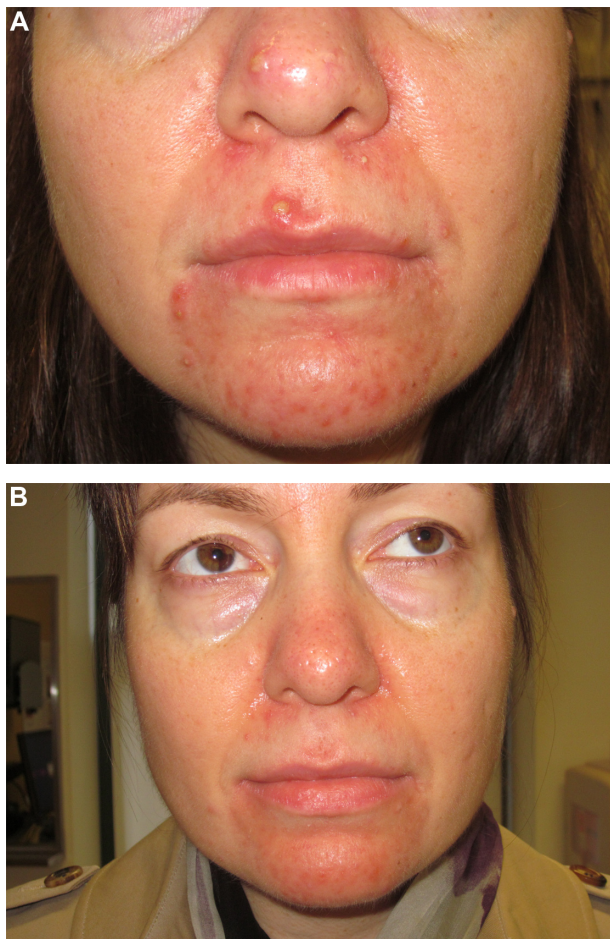


Figure 7 (A) Severe perioral dermatitis (a version of acne-rosacea). **(B)** Dramatic improvement after initiation of oral isotretinoin.

Note: Full clearance with no recurrence was seen after 20 weeks of therapy.

often beneficial to combine vascular laser treatments and oral isotretinoin. Contrary to historical belief, there is no increased risk of scarring or abnormal wound healing with this combination, and both symptoms of rosacea and central facial erythema and telangiectasia can be reduced dramatically. Many reports of skin sensitivity or fragility while on isotretinoin have been reported, which is a real concern.^{70,71} Therefore, patient education is important before initiating therapy with regards to facial or body waxing, scratching or picking, and exposure to extremes of temperature (hot tubs, steam rooms, skiing) as these can predispose to easier skin trauma. Atypical keloid formation has also been documented following dermabrasion while on isotretinoin.^{72,73} However, recent controlled investigations have analyzed skin healing in patients on oral isotretinoin therapy and have debunked previous concerns.

One comparative retrospective study assessed the effect of invasive acne scar treatment and laser hair removal in a group of 55 patients on a combination of topical therapy and isotretinoin 0.5 mg/kg daily compared with a group of

55 patients on topical monotherapy.⁷⁴ Notably, there were no differences between the two groups with regard to adverse outcomes, with no development of keloids, atypical scarring, or delayed wound healing following laser therapy. No complications were seen in 35 patients taking isotretinoin 10 mg/kg daily for at least one month prior to a mean of 3.1 sessions with 1,550 nm erbium-doped fiber laser therapy.⁷⁵

Finally, oral zinc sulfate has been proposed as an additional oral treatment for rosacea. In a randomized, controlled, double-blind, crossover study of 19 patients receiving 100 mg zinc sulfate capsules or placebo three times daily, significantly reduced scores were seen in both treatment arms during the zinc treatment arm, with a relative plateau during the placebo phase.⁷⁶ In contrast, a similar trial of 220 mg zinc sulfate dosed twice daily showed no difference in patients receiving zinc therapy versus placebo.⁷⁷ Neither of the studies on oral zinc products produced any side effects of concern. Since both studies did not account for rosacea subtypes, future studies should focus on precise data collection to determine which subtypes, if any, are benefited most by the antioxidant and anti-inflammatory properties of zinc.

Lasers and lights

Many lasers have created a paradigm shift in the treatment of erythema and telangiectasias associated with rosacea. Those most commonly used include the pulsed dye laser (PDL, 585–595 nm), intense pulsed light (IPL, 500–1,200 nm), potassium titanyl phosphate (KTP, 532 nm) laser, and long-pulsed neodymium:yttrium-aluminum-garnet laser (Nd:YAG, 1,064 nm).^{78–82} Carbon dioxide (CO₂) and erbium:yttrium-aluminum-garnet (Er:YAG) induce drastically higher target temperatures resulting in vaporization, and are therefore implemented in ablative correction of rhinophyma and other manifestations of phymatous rosacea. The older generation of argon, copper bromide, and krypton lasers paved the way for new lasers and lights developed specifically for cutaneous vascular lesions with more precision to minimize such side effects as hypopigmentation, atrophic scars, and recovery time.^{83,84} Laser settings used in major studies of the treatment of rosacea with prominent telangiectasia and erythema (Table 2) and phymatous rosacea (Table 3) are outlined in detail, with laser manufacturers listed when specified by the authors. An in-depth review of all the published studies using lasers and/or lights for the treatment of rosacea is beyond the scope of this current review.

Pulsed dye laser

PDL historically emitted light at 577 nm and more recently at 585 nm or 595 nm, all wavelengths that closely correspond

Table 2 Data from nonablative laser and light studies in rosacea treatment

Device	N (n)	λ (nm)	Ø (mm)	Pulse (msec)	Fluence (J/cm ²)	Treatments (n)	Treatment interval	Follow-up	Reference (laser manufacturer)
PDL	8	577	3	0.0003	0.5–5	1	–	24 and 48 hours	Anderson and Parish ⁷⁸ (SLL-I 100, Candela Corporation, Wayland, MA, USA)
	27	585	5	0.450	6.0–7.5	1–3	6–12 weeks	6–8 weeks	Lowe et al ⁸⁸ (SPTL-I, Candela Corporation)
	20 (17)	590–595	2×7	1.5	15–20	1–2	8 weeks	4, 8, 12, and 24 weeks	West and Alster ¹¹⁷ (versus KTP) (ScleroPlus, Candela Corporation)
	13 (11)	595	7	10	9.5 (p), 8.0 (np)	1	–	1 and 6 weeks, 3 and 6 months	Alam et al ⁸⁹ (V-Beam, Candela Corporation)
	12	595	7	6	7–9	1	–	6–8 weeks	Jasim et al ⁹⁰ (V-Beam, Candela Corporation)
	40 (35)	585	5 or 7	0.45	5.4–6.5	1–10	NR	Mean 23.3 months	Tan et al ⁹² (Photogenica V, Cynosure Inc., Westford, MA, USA)
	32	585	5	0.45	6–6.75	1	–	3 months	Lonne-Rahm et al ⁹³ (NR)
	16	595	7	1.5	9.5–11.5	2	8–10 weeks	2 months	Tan and Tope ⁹¹ (V-Beam, Candela Corporation)
	20 (17)	595	T: 3×10, E: 12	T: 40, E: 3	T: 17–19, E: 6.0–7.0	4	4 weeks	2 months	Bernstein and Kligman ⁸⁷ (V-Beam, Candela Corporation)
	3	595	10	10	7.5	3	2 weeks	4 and 12 weeks	Togsverd-Bo et al ⁹⁴ (V-Beam Perfecta, Candela Corporation)
	21 (18)	595	5–12	NR	5.75–13.25	1	–	6–12 weeks	Langigan ⁹⁷ (V-Beam, Candela Corporation)
	26	595	10	6	7	3	4 weeks	4 weeks	Neuhaus et al ¹⁰⁷ (versus IPL) (V-Beam, Candela Corporation)
	1	585	7	0.5	4.9–5.8	3	NR	12 months	Moreira et al ¹³¹ (NR)
	18 (15)	585	7	10	7–9	3	3 weeks	6 weeks	Kim et al ⁹⁵ (Cynergy, Cynosure Inc.)
	20	595	7	1.5–40	7.75–9.0	3	6–8 weeks	NR	Shim and Abdullah ⁴⁹ (V-Beam Perfecta, Candela Corporation, Syneron Medical Ltd, Yokneam, Israel)
IPL	15	595	7	6	12	3	4 weeks	1 month	Salem et al ¹¹⁹ (versus Nd:YAG) (V-Beam, Candela Corporation)
	16 (14)	595	10	6	7.5	4	3–4 weeks	1 month	Alam et al ¹²⁰ (versus Nd:YAG) (V-Beam, Candela Corporation)
	200 (188)	≥550 (I–II) ≥570 (II–III)	NR	2.5–6.0	36–45	1–4	NR	2 months	Angermeier ⁹⁹ (PhotoDerm VL; ESC Medical Systems, Yokneam, Israel)
	32 (28)	≥560, ≥570	450×100, 150×80	2.4/4.0**	27–32, 32–36	Mean 3.6	≥3 weeks	Mean 3.7 months	Taub ¹⁰⁰ (Vasculight Plus/Vasculight SR, Lumenis Corp)
	4	≥515	NR	3	22–25	5	3 weeks	1 month	Mark et al ¹⁰¹ (Photoderm VL, Lumenis, Needham, MA, USA)
	60	≥550 (93%)	8×35	4.3–6.5	25–35	Mean 2.1	NR	1, 2, 4, and 12 weeks, mean 51.6 months	Schroeter et al ¹⁰² (Photoderm VL and Vasculight)
	34 (28)	≥560	34×8	2.4/4.0* (I–II) 2.4/5.0* (III) 2.4/6.0* (IV)	24–32	4	3 weeks	6 months	Papageorgiou et al ¹⁰³ (Quantum SR, Lumenis, London, UK)
	21	470–980	NR	13, 3×4	23–36	5	1 month	1 and 3 months	Taub and Devita ¹⁰⁶ (Aurora SRA, Syneron Medical Ltd)
	5	≥560	NR	NR	29–30	1	–	None	George et al ¹¹⁸ (versus KTP) (Quantum IPL)

(Continued)

Table 2 (Continued)

Device	N (n)	λ (nm)	\emptyset (mm)	Pulse (msec)	Fluence (J/cm^2)	Treatments (n)	Treatment interval	Follow-up	Reference (laser manufacturer)
	26 (25)	≥ 560	NR	2.4/6.0*	25 (+1, as tolerated)	3	4 weeks	4 weeks	Neuhaus et al ¹⁰⁷ (versus PDL) (Quantum, Lumenis, Santa Clara, CA, USA)
	102	≥ 420 (w/acne) ≥ 530 (w/o)	10 \times 40	2.5–5	10–20 (w/acne), 10–30 (w/o)	Mean 7.2	1–3 weeks	1–3 weeks	Kassir et al ¹⁰⁴ (NaturalLight, Focus Medical, Bethel, CT, USA)
	30	540–950	640 \times 640	12	10–12	3	3 weeks	3 weeks	Liu et al ¹⁰⁹ (Lovely II, Alma Lasers Ltd, Caesarea, Israel)
	50	≥ 560	NR	6–7	12–16	4	3 weeks	NR	Lim et al ¹¹⁰ (Rex-Prime, Union Medical, Ulsjeongbu, Korea)
	3	≥ 500 –635	6.35	14	20–22	2, 16, and 18	4 weeks	6 months	Tsunoda et al ¹¹¹ (AcuTip 500, Cutera, Brisbane, CA, USA)
KTP	20 (17)	532	1	10	15	1–2	8 weeks	4, 8, 12, and 24 weeks	West and Alster ¹¹⁷ (versus PDL) (Aura, Laserscope, San Jose, CA, USA)
	204	532	2	10–14	10–12	1–9	6 weeks	6 weeks	Clark et al ¹¹⁵ (Aura, Laserscope UK, Gwent, UK)
	5	532	NR	NR	13	1	–	None	George et al ¹¹⁸ (versus IPL) (Gemini, Laserscope)
	647 (452)	532	1–4	11–12	11–12	2–3	6 weeks	Every 6 weeks	Becher et al ¹¹⁴ (Aura, Laserscope UK)
Nd:YAG	15	1,064	18	10	22	3	4 weeks	1 month	Salem et al ¹¹⁹ (versus PDL) (Gentle YAG, Candela Corporation)
	16 (14)	1,064	8	0.3	6	4	3–4 weeks	1 month	Alam et al ¹²⁰ (versus PDL) (Genesis Module, Excel V, Cutera)

Notes: *Double pulse with 15.0 msec delay; **double pulse with 20 msec delay.

Abbreviations: \emptyset , spot size; N, number of patients treated; n, number of patients who completed follow-up; λ , wavelength; NR, value not reported; T, telangiectasia; E, erythema; p, purpuragenic; np, nonpurpuragenic; I, II, III, Fitzpatrick skin types; w, with; w/o, without; Nd:YAG, neodymiumyttrium-aluminum-garnet laser; PDL, pulsed dye laser; IPL, intense pulsed light; KTP, potassium titanyl phosphate.

Table 3 Data from studies on ablative lasers in the treatment of phymatous rosacea

Device	n	∅ (mm)	Delivery	Power or fluence	Treated (n)	Treatment interval	Follow-up	Reference (laser manufacturer)
CO ₂ (λ: 10,600 nm)	4	1–2	Continuous	10–50 W	4	NR	6 months	Shapshay et al ¹²⁶ (NR)
	6	5	NR	10 W	1–2	“Few months”	1 year	Goon et al ¹²⁸ (NR)
	124	4–7	Resurfacing	20–40 W	1 (n=115), 2 (n=8) and 4 (n=1)	NR	3 months	Maden et al ¹²⁷ (Sharplan 40C CO ₂ laser SilkTouch/FeatherTouch scanner, Sharplan Lasers UK Ltd, London, UK)
	4	1–3	Continuous	10–20 W	NR	NR	NR	Cravo et al ¹²⁹ (NR)
	9 (7)	1.2–3.0	Continuous	6–8 J/cm ²	1	–	1 month, 1 year	Lim ¹²² (Sharplan 40C CO ₂ laser SilkTouch/FeatherTouch scanner, Sharplan/ESC Laser Inc., Allendale, NJ, USA)
	1	NR	NR	20–30 W	1	–	7 months, 19 months	Moreira et al ¹³¹ (NR)
	1	6	Continuous	NR	5	2–3 months	3 months	Rai and Madan ¹³⁰ (Sharplan 40C CO ₂ laser)
	541	Variable	50–100 Hz	18 W	1×6 passes	–	Variable	Campolmi et al ¹²⁵ (Smart Xide Laser, DEKA-MELA, Calenzano, Italy)
	14	3	100 Hz	6–7 W	Variable	Variable	3 years	Carradino et al ¹³⁴ (NR)
	3	15	Fractionated, 20%–50%	2.5–10 W	1×4–6 passes	–	3 months	Singh et al ¹³³ (fractionated CO ₂ laser, Sola Medical, Hayward, CA, USA)
Er:YAG (λ: 2,940 nm)	22	0.1	Continuous	40–70 mJ/pulse	1	–	3–18 months	Lazzeri et al ¹³⁶ (NR)
	5	NR	Fractionated	7.5–10 W	1	–	1, 4, and 6 weeks	Serowka et al ¹³² (Fraxel re:Pair, Solta Medical)
	24	NR	70% density	70 mJ	1×16–18 passes	–	3 weeks	Bassi et al ¹³⁵ (Smart Xide laser DEKA-MELA)
	6	5	50–80, then 10 Hz	5–25, then 1 W	2–6	3 weeks	1–2 years	Orenstein et al ¹³⁷ (Derma TM20 Er:YAG laser, ESC Medical Systems, Yokneam, Israel)
	6	5	10 Hz	1.2 J	1×≤10 passes	NR	1 year	Goon et al ¹³⁸ (NR)
	6	5	NR	1.2 J	1–2	“Few months”	7, 21, 45, 90 days	Fincher and Gladstone ¹³⁹ (Contour, Sciton Inc., Palo Alto, CA, USA)
	6	3	Spot and scanner	25 J/cm ²	1×4 passes	–	–	–

Notes: *Double pulse with 15.0 msec delay between first and second pulses.

Abbreviations: ∅, spot size; n, number of patients treated; λ, wavelength; NR, value not reported; Er:YAG, erbium:yttrium-aluminum-garnet.

with the absorption peak of oxyhemoglobin and thus target superficial vasculature.^{78,85} Post-treatment purpura was a disadvantage of classic PDL treatments, but has been minimized in modern studies.⁸⁶ The latest generation of PDL utilizes longer pulse durations and has the ability to emit variable energies that specifically target telangiectasias with less purpura and dyspigmentation than previously (“subpurpuric dosing”).^{87–89}

PDL has been shown to improve both the clinical findings of rosacea (erythema, telangiectasia) as well as the associated symptoms.^{87–97,107,117} In one study, after verifying sensitivity with a provocative lactic acid test, 32 patients with rosacea were treated with one session of 585 nm PDL.⁹³ Thirty-one patients who were stinger positive before treatment showed decreased scores after treatment, and one patient had the same stinger test score before and after treatment. In addition, biopsies taken before and 3 months after treatment were analyzed immunohistochemically for changes in substance P, calcitonin gene-related peptide, and vasoactive intestinal polypeptide, all of which are neuropeptides implicated in microvascular pathophysiology. Dermal papillae demonstrated a statistically significant reduction in the number of substance P-positive nerve fibers; however, no effect was seen on either vasoactive intestinal polypeptide or calcitonin gene-related peptide immunoreactivity. This finding highlights substance P as a potential key player in the pathophysiology of the vascular changes prominent in rosacea and responsive to PDL therapy.

Intense pulsed light

IPL has been shown to be applicable in various clinical settings, including rosacea, port wine stains, disseminated porokeratosis, seborrheic keratosis, sarcoidosis, and hypertrophic keloid scars.⁹⁸ Parameter flexibility enables the targeting of deep vessels, as well as large areas of telangiectasia, erythema, and flushing, but does require clinical expertise and experience to perfect treatments and decrease complications. Most IPL systems provide a large spot size, reducing patient discomfort, increasing efficiency of treatment, and enabling deeper light penetration. When used appropriately, IPL appears to provide impressive results in various settings with a relatively negligible side effect profile.^{97–111}

Early on, Angermeier demonstrated 75%–100% clearance after one or two treatments in 174 of 188 patients with vascular lesions at a 2-month follow-up.⁹⁹ Soon after, these same results were confirmed in a study specific to rosacea only.¹⁰⁰ Thirty-two patients treated with double-pulsed IPL for an average of 3.6 times with at least 3-week intervals achieved improved redness (83%), flushing and

texture (75%) and acneiform breakouts (64%) subjectively at 3–4-month follow-up self-assessments. Notably, very few patients experienced purpura (n=1), peeling (n=1), or post-inflammatory hyperpigmentation (n=1).

IPL demonstrated a decrease in blood flow (30%), a decrease in surface area of telangiectasias (29%), and a decrease in the intensity of erythema (21%) in one study using a 510 nm filter.¹⁰¹ This implies that IPL treatments have a clinically relevant effect on the local cutaneous vasculature, which is central to the symptomatology seen in patients with rosacea.

Taub et al tackled the persistent background erythema often remaining after effective targeted therapy of telangiectasia in patients with ETR.¹⁰⁶ Twenty-one patients with ETR received five monthly facial treatments of a electro-optical synergy device combining pulsed light (470–980 nm) with bipolar radiofrequency (Elos, Syneron). The electro-optical synergy parameters were complex, with a combination of short pulses (13 msec light and 80 msec radiofrequency) performed horizontally and long pulses (12 msec light and 85 msec radiofrequency) performed vertically. Outcome measures of erythema and telangiectasia were assessed by clinicians comparing before and after photographs in addition to self-assessment scores. Significant improvement was achieved in both erythema and telangiectasia assessed by both physicians and patients at all follow-up intervals. Notably, patients reported significant improvement in flushing, one of the most psychosocially challenging disease manifestations.

Of note, IPL (560 nm filter) has been compared with nonpurpuric (6 msec) PDL in a head-to-head, randomized, controlled, split-face trial, and it was found that both treatment modalities demonstrated similar efficacy in improving erythema and telangiectasia in 29 patients with ETR.¹⁰⁷

Potassium-titanyl phosphate laser

Ideal for linear, arborizing, and discrete telangiectasia, KTP laser, a product of the 1,064 nm yttrium-aluminum-garnet laser family, results from passing Nd:YAG light through a KTP crystal that halves the wavelength, producing a 532 nm green light. Emitting light twice the frequency of Nd:YAG, KTP interacts with superficial chromophores, making it quite useful for superficial vessels and with less healing time.^{112–117} Although beneficial for such lesions, such low wavelengths have the disadvantage of interacting with melanin and are limited to lighter skin tones due to the risk of post-inflammatory hyperpigmentation. With minimal discomfort, KTP can target vessels 1–3 mm below the skin surface, and increasing pulse widths enable treatment of vessels of larger diameter. Some recommend cooling the skin with chilled water-based gel and utilizing post-treatment ice,

basing each treatment session off an endpoint when vascular lesions appear grayish and are no longer readily visible.¹¹³

PDL (595 nm, 1.5 msec) and KTP was studied head-to-head in 20 female patients with facial or leg telangiectasias.¹¹⁷ Photographs taken before treatment and on four different follow-up visits were scored on a five-point scale (zero to four) by the patient and a blinded physician and nurse in addition to patient-rated 10-point pain scores. Twelve weeks after one to two treatments, PDL resulted in an average telangiectasia improvement score of 3.1 in the lower extremities and 3.8 on the face compared with 1.8 and 2.3 for lesions treated with KTP on the five-point efficacy scale. Despite the clearly superior efficacy of PDL in this study, patients noted significantly more pain, hyperpigmentation, and purpura lasting up to 2 weeks, and therefore may prefer multiple KTP treatments. KTP has also been studied against IPL, with clinical improvements demonstrated for both, but with a significant skin temperature rise immediately after KTP as compared with no change in skin temperature after IPL.¹¹⁸

Neodymium:yttrium-aluminum-garnet laser

Long-pulsed Nd:YAG is efficacious in the treatment of large deep vessels with blue tones.¹¹² When evaluated in a split-face comparative study of 15 patients with ETR, both long pulsed Nd:YAG (1,064 nm) and short wavelength PDL yielded comparative responses with regard to erythema and telangiectasia.¹¹⁹ This laser is not as commonly used in rosacea because larger blue veins or deep vascular networks are rarely present, but are useful for dilated leg or facial veins or recalcitrant vascular malformations/port wine stains.

CO₂ laser and erbium:yttrium-aluminum-garnet laser

Many consider ablative lasers such as CO₂ (10,600 nm) and Er:YAG (2,940 nm) as first-line treatment options for rhinophyma; however, various other surgical techniques have been shown to improve disfigurement, including cold steel, hot loop/radiowave and scalpel excision, electrosurgery, dermabrasion, and cryosurgery.^{120–139} All may be cosmetically limited due to excessive intraoperative bleeding obstructing visualization and causing imprecise tissue removal, along with the risk of scarring. Technological enhancements such as scanned and “superpulsed” systems emit shorter pulses with high power, reducing common adverse effects such as scarring and dyspigmentation. Ablative laser therapy can be used to contour the deformed nasal shape by partial excision of the sebaceous follicle to the bases. Despite transient swelling, erythema, and crusting which require longer healing times than nonablative lasers and risk permanent dyspigmentation,

textural changes, and scarring, the ultimate results can be cosmetically and psychosocially life-changing in just one or two treatments (Figure 8).

Clinical challenges: combination therapy and managing erythema in rosacea

Since rosacea is a chronic inflammatory condition, it is uncommon for a single treatment to effect a permanent cure, and many frequently fall short of dramatic improvement. In mild

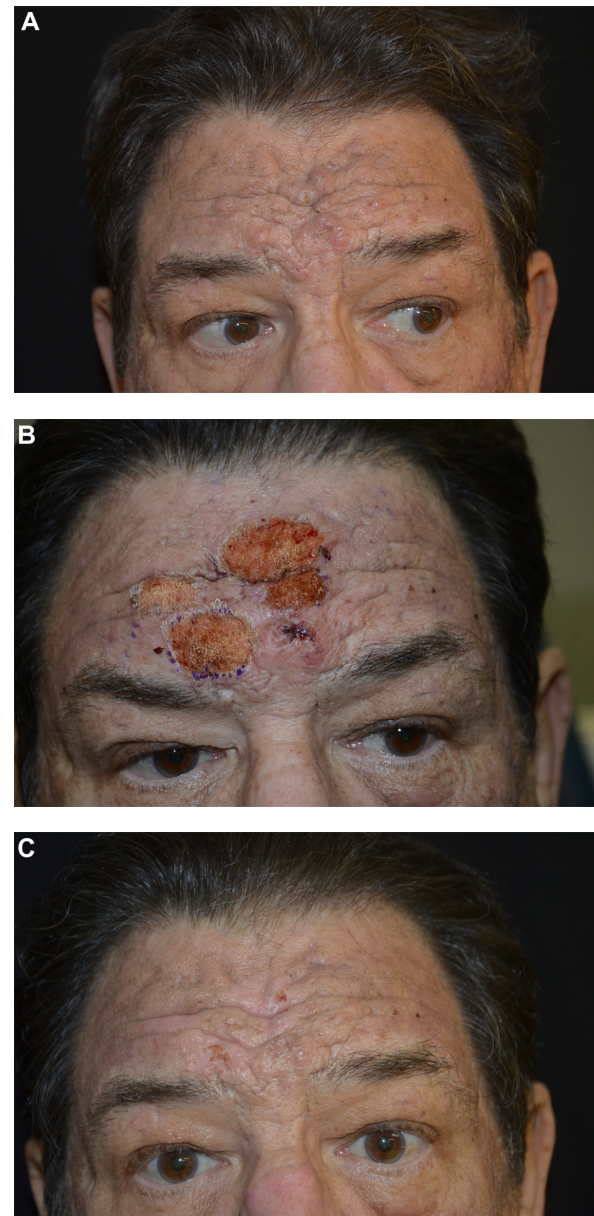


Figure 8 Before (A) and immediately after (B) continuous wave fully ablative carbon dioxide laser treatment, and 2 weeks following (C) treatment for metapophyma (enlargement of sebaceous glands on the forehead).

Notes: Dramatic improvement without any sequelae is seen in the areas of concern for this patient. Similar results are seen with rhinophyma using comparable methods.

disease, topical treatments and lifestyle modification may be adequate. Most patients, however, have only slight responses to monotherapy and combination approaches are generally required. Erythema and telangiectasias are best treated by laser and light therapies, and often require combination with oral tetracyclines and topical immunotherapy and/or brimonidine topical gel (Mirvaso®). PPR often responds to a combination of oral tetracyclines with topical metronidazole, but if recurrent, recalcitrant, or severe, may require oral prednisone or isotretinoin. As previously stated, rhinophyma requires surgical or laser interventions for best results. Although oral isotretinoin has been reported to help sebaceous hyperplasia permanently, in the opinion of the senior author (JE) this is not seen in rhinophyma. A recent case report utilizing low-dose isotretinoin (20 mg daily for one year, followed by 10 mg daily for an additional year) prevented troublesome recurrence following CO₂ ablation for a 20-year history of sebaceous hyperplasia in a 55-year-old Korean man.¹⁴⁰

Sebaceous hyperplasia has also troubled transplant patients on immunosuppression. Two cases of cyclosporine-induced sebaceous hyperplasia resolved 3 months after treatment with 10 or 20 mg isotretinoin daily.¹⁴¹ No side effects, drug interactions, or transplant-associated complications were experienced. Higher doses of isotretinoin (40 mg each morning and 20 mg each evening) were used to treat refractory sebaceous hyperplasia in a 57-year-old Caucasian female, with reduction in lesion size after one month which was nearly complete by 2 months.¹⁴² Despite these case reports, in our experience, rhinophyma requires surgical or laser intervention for a cure.

Most importantly, physicians must assess patient concerns and expectations at the first visit and educate about the condition, the long-term treatments required, and the at-home compliance and skin care (gentle cleansing, moisturizing, and photoprotection) needed for best results.¹⁴³

Pathophysiological changes in the erythematous and sebaceous skin of rosacea might differ between patients, yielding nonuniform treatment responses. For example, the vasculature involved in erythematous manifestations could be enlarged, thickened, dilated, or even newly formed, and conventional therapies may only target one dimension of these pathological changes. Thus, multiple modalities are often required and may not yield a permanent cure, but require lifelong maintenance after initial improvement.

Patient-focused perspectives: quality of life and patient satisfaction

As stated earlier, there is a significant burden on the quality of life (QoL) in patients with rosacea, not only cosmetically due

to their unwanted appearance but also due to the painful and irritating symptoms associated with the condition. Rosacea patients present with higher rates of anxiety and depression, develop greater general symptom intensity, experience difficulty functioning in everyday life, perceive general health more negatively, and subjectively feel they receive poor social support.¹⁴⁴ They experience not only high loads of stress, but also embarrassment and social phobia as a result of their skin condition. Contrary to historical belief, rosacea patients have the highest comorbidity of depression, while alcohol abuse has a very mild association.¹⁴⁵

Clinical trials have tried to measure outcomes by improvement in patient QoL, which may be assessed by various standardized questionnaires, such as the Dermatology Life Quality Index (DLQI), Skindex-29, and rosacea-specific QoL indices. The DLQI questionnaire is a reliable and valid instrument that is quite sensitive to QoL changes brought about by various treatment options.^{146,147} The rosacea-specific QoL and Skindex-29 measure which characteristics of rosacea affect the patient's life the most. Interestingly, flushing was found to be the most troubling symptom reported by patients affected by rosacea, stressing the importance of treating both the cosmetic and medical aspects of this condition.¹⁴⁸

The DLQI questionnaire evaluates QoL with ten questions covering the feelings, daily activities, clothing, physical or social activities, exercise, education or job, relationships, and treatments impacted by dermatological conditions. Developed in 1994, this measure has been utilized in the study of a variety of diseases, including rosacea. Variables are scored by patients on a Likert scale and final results range from 0 to 30, with higher numbers signifying more extreme effects on a patient's QoL. Tan and Tope first applied this outcome measure to 16 ETR patients treated with PDL, and demonstrated a significant reduction from 7.8 to 1.9 at 2 months following two laser treatment sessions.⁹¹ When measured in 20 patients before and after 595 nm PDL treatment, averaged DLQI scores decreased from 17.3 to 4.3, indicating a significant improvement in QoL from the patient perspective.¹⁴⁹ Finally, Menezes et al used this index to assess the impact of PDL in a prospective study of 22 patients with ETR and found a significant reduction from 5.6 before treatment to 1.5 after three treatment sessions.¹⁵⁰

Recommendations

Systemic isotretinoin therapy

As previously discussed, isotretinoin is a viable alternative for recalcitrant cases of rosacea. In a large-scale, placebo-controlled, randomized, 12-week, multicenter study,

Gollnick et al demonstrated complete remission in 24% and marked improvement in 57% of patients with isotretinoin 0.3 mg/kg therapy daily, in contrast with remission in 14% and marked improvement in 55% of patients treated with doxycycline 100 mg daily for 14 days, then 50 mg daily. Patients treated with isotretinoin rated treatment results at the end of the study as “excellent improvement” more frequently, at 32.6% in comparison with 24.2% for patients treated with doxycycline.⁶⁷

OnabotulinumtoxinA injections

Anecdotal results of reduced erythema and acne with the use of OnabotulinumtoxinA (Botox®, Allergan, Irvine, CA, USA) for cosmetic purposes led Dayan et al to experiment further in 13 patients with rosacea.¹⁵¹ Over the course of 2 years, patients received intralesional microdroplet injections (0.05 mL) of onabotulinumtoxinA in a dilution of 7 mL of saline solution per 100 units. The results indicated significant reduction in erythema and flushing of the affected area 2–4 weeks after treatment. Their predecessors reported similar results after a 26-year-old male was injected with 10 units of onabotulinumtoxinA at 1 cm intervals into one cheek.¹⁵²

Excel V laser: combining KTP and Nd:YAG

The new Excel V laser combines KTP and Nd:YAG, two previously discussed lasers with different wavelengths. KTP emits light at a wavelength of 532 nm, which targets redness, hyperpigmentation, and damaged capillaries at the surface of the skin, while Nd:YAG has a laser wavelength of 1,064 nm designed for treating more deep blood vessels with larger diameters. Following absorption of energy, abnormal blood vessels are thermosealed while hyperpigmented lesions are fragmented, resulting in an overall improved appearance.

Conclusion

Rosacea is a chronic inflammatory condition without a permanent cure. Recent advances in combination treatments offer treatments with better initial results and longer-term maintenance than in the past. The fundamental key for successful management of rosacea is based on identification of the specific subtype, understanding the severity of presentation, and tailoring treatments to best suit the expectations of the patient. Continued research into both the cosmetic and medical aspects of this condition will further define treatment protocols that ultimately will refine the current options available to patients.

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Disclosure

The authors report no conflicts of interest in this work.

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