




## REVIEW ARTICLE

# Rosacea management: A comprehensive review

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## Abstract

Rosacea is a chronic cutaneous disorder affecting primarily the face, characterized by erythema, transient or persistent, telangiectasia, and inflammatory lesions including papulo-pustules and swelling. The essential component of the disease is the persistent erythema of facial skin. Episodes of flushing (acute-subacute intermittent vasodilation) are common. Swelling and erythema of the nose along with dilatation of the pilosebaceous poral orifices, known as rhinophyma, can be noted in chronic cases. Rosacea affects up to 10% of the world population and is especially noted in fair-skinned individuals aged 35–50. Women are affected more often than men. Several treatment modalities including topical medications, systemic drugs, lasers, and light-based therapies have been used for the management of rosacea with variable results. Topical medications such as azelaic acid, metronidazole, and sulfacetamide/sulfur, oral antibiotics such as tetracyclines, and oral retinoids alone or, most commonly, in combination form the mainstay of treatment. Light therapies such as intense pulsed light and pulsed dye laser are best used for the erythemato-telangiectatic type. Topical brimonidine, oxymetazoline, ivermectin, tacrolimus, pimecrolimus, low-dose modified-release tetracyclines and botulinum toxin are the new additions to the therapeutic armamentarium. This article provides a comprehensive review of the various therapies used for rosacea.

## KEYWORDS

brimonidine, doxycycline, IPL, PDL, rosacea

## 1 | INTRODUCTION

Rosacea is a chronic, relapsing, inflammatory dermatosis affecting predominantly facial convexities such as the cheeks, nose, forehead, and the chin.<sup>1</sup> It affects up to 10% of the world population with women being affected more often than men.<sup>2</sup> However, rhinophyma is noted primarily in males. Although the peak age for incidence and severity of the disease is in the twenties to forties of any skin type,

it may affect individuals of any age. The incidence of rosacea varies among ethnicities, affecting most commonly fair-skinned persons, that is, skin phototypes I and II, followed by Asians and dark-skin persons.<sup>3</sup>

The classification and staging for rosacea developed by National Rosacea Society Expert Committee (NRSEC) is used in practice across the world.<sup>4,5</sup> The diagnosis of rosacea is suggested by the presence of one or more features with a central facial distribution

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(Table 1).<sup>4</sup> The constellation of primary and secondary features of rosacea forms four patterns or disease subtypes (Table 2).<sup>4</sup> Many patients may present with more than one subtype.

The NRSEC also developed a standard clinical grading scorecard (Table 3)<sup>5</sup> to assess the severity of rosacea and compare the research data from different sources.

The pathophysiology and molecular biology of the rosacea remains largely ambiguous, and the clinical and histopathological findings suggest involvement of various inflammatory and immune-mediated processes. There seems to occur an early and aggravated immune response which induces abnormal cathelicidin peptides, promotes, and regulates leukocytic chemotaxis, angiogenesis, and expression of extracellular matrix proteins. Aberration in cutaneous vascular homeostasis has also been suggested. There is also reactive oxygen species (ROS) induced damage to keratinocytes, fibroblasts, and endothelial cells by the release of interleukin (IL)-1 and tumor necrosis factor (TNF)- $\alpha$ . UVR and sunlight is well known to induce erythema and worsen other clinical symptoms. Exposure to UVA results in decreased activity of MMPs involved in degradation and

remodeling of dermal matrix and inhibition of collagen synthesis. UVB exposure leads to the production of various immunomodulatory cytokines (IL-1, IL-4, IL-6, IL-8, IL-10, and TNF $\alpha$ ) and angiogenic factors like VEGF. Elevated levels of various proteases like serine protease kallikrein 5 (KLK5) have also been reported in rosacea.<sup>6</sup>

Microbes such as *Demodex folliculorum* and *Helicobacter pylori* are also implicated as triggers in some of the cases. Rosacea may rarely also develop as a manifestation of systemic diseases. Obesity, smoking, and inflammatory bowel disease are significant risk for the development of this disease. In addition, metabolic, neurologic, psychiatric disorders and certain malignancies, drugs, and dietary elements also show a significant association with rosacea.

## 2 | MANAGEMENT

Several therapeutic modalities used to treat rosacea have yielded variable outcomes due to the complex pathogenesis of the disease. Patient education, establishing a skin care routine, pharmacotherapy

TABLE 1 Primary and secondary clinical features of rosacea

Types	Clinical features	Description
Primary features	Flushing (transient erythema)	History of frequent blushing or flushing
	Non-transient erythema	Persistent redness of facial skin (most common sign)
	Papules and pustules	Dome-shaped red papules with or without accompanying pustules, often in crops, and occasional nodules
	Telangiectasia	Common but not necessary for the diagnosis
Secondary features	Burning or stinging	Burning or stinging sensations with or without scaling or dermatitis especially on malar area
	Plaque	Erythematous plaques without epidermal changes in the surrounding skin
	Dry appearance	Central facial skin may be rough and scaly resembling dry skin. This "dryness" may be associated with burning or stinging sensations and may be caused by irritation rather than the disease
	Edema	May accompany or follow prolonged facial erythema or flushing. A sense of fullness of cheeks and a subtle induration of the cheeks on examination can occur. Sometimes soft edema may last for days
	Ocular manifestations	Range from symptoms of burning or itching to signs of conjunctival hyperemia and lid inflammation. Styes, chalazia, and corneal damage may occur
	Peripheral location	Rosacea may occur at other sites, but the frequency and occurrence of this are ill-defined. It may or may not be accompanied by facial manifestations
	Phymatous changes	These include patulous follicles, skin thickening or fibrosis, and a bulbous appearance. Rhinophyma is the most common form

TABLE 2 Clinical subtypes of rosacea

Clinical subtypes	Description
Erythematotelangiectatic	Flushing and persistent central facial erythema with or without telangiectasia
Papulopustular	Persistent central facial erythema with transient, central facial papules or pustules or both
Phymatous	Thickening of skin, irregular surface nodularities, and enlargement. It may occur on the nose, chin, forehead, cheeks, or ears
Ocular	Foreign body sensation in the eye, burning or stinging, dryness, itching, ocular photosensitivity, blurred vision, telangiectasia of the sclera or other parts of the eye, or periorbital edema
Other variants	Granulomatous; non-inflammatory; hard; brown, yellow, or red cutaneous papules; or nodules

with topical and oral medications to control flare-ups, and lasers/light-based therapies constitute the mainstay of rosacea management. Treatment needs to be customized, and combination of different modalities is most often required for managing the variable signs and symptoms of rosacea.<sup>7</sup>

## 2.1 | Topical therapies

The choice of topical agents is based on factors such as skin type, predominant signs and symptoms, mechanism of action, efficacy and tolerability of the drug and past treatment. The components of the vehicles of commonly used topical formulations for papulopustular rosacea are highly important in the delivery of the active ingredient, tolerability of therapy, and patient compliance.

US Food and Drug Administration (FDA)-approved topical therapies for rosacea are<sup>8</sup>:

- Azelaic acid (15%) gel
- Metronidazole (0.75% gel, cream, and lotion, and 1% cream and gel)
- Sodium sulfacetamide/sulfur (10%/5%) gel, cleanser, lotion, suspension, and cream

TABLE 3 Rosacea clinical scorecard

	Severity
<b>Primary features</b>	
Flushing (transient erythema)	Absent/ Mild/ Moderate/ Severe
Non-transient erythema	Absent/ Mild/ Moderate/ Severe
Papules and pustules	Absent/ Mild/ Moderate/ Severe
Telangiectasia	Absent/ Mild/ Moderate/ Severe
<b>Secondary features</b>	
Burning or stinging	Absent/ Mild/ Moderate/ Severe
Plaques	Absent/ Mild/ Moderate/ Severe
Dry appearance	Absent/ Mild/ Moderate/ Severe
Edema	Absent/ Mild/ Moderate/ Severe
If present	Acute/ Chronic
If chronic	Pitting/ Nonpitting
Ocular manifestations	Absent/ Mild/ Moderate/ Severe
Peripheral location If present: List location(s)	Absent/ Present
Phymatous changes	Absent/ Mild/ Moderate/ Severe
<b>Global assessment</b>	
<b>Physician ratings by subtype</b>	
Subtype 1: Erythematotelangiectatic	Absent/ Mild/ Moderate/ Severe
Subtype 2: Papulopustular	Absent/ Mild/ Moderate/ Severe
Subtype 3: Phymatous	Absent/ Mild/ Moderate/ Severe
Subtype 4: Ocular	Absent/ Mild/ Moderate/ Severe
<b>Patient's global assessment</b>	
Total score:	Absent/ Mild/ Moderate/ Severe

- Brimonidine tartrate (0.33%) gel
- Oxymetazoline hydrochloride (1%) cream
- Ivermectin (1%) cream

Other topical medications, such as the calcineurin inhibitors (tacrolimus and pimecrolimus), benzoyl peroxide, and topical antibiotics (clindamycin and erythromycin), are used as second-line agents.

## 2.2 | Azelaic acid (AzA)

Azelaic acid, a natural dicarboxylic acid, is approved by FDA as 15% gel for treating mild-to-moderate rosacea. It exerts its therapeutic effect of reduction in erythema and inflammatory lesions by inhibiting NADPH oxidase activity on the neutrophilic cell membrane, thereby decreasing the reactive oxygen species (ROS) activity. The usefulness of AzA in rosacea especially of PPR subtype is well established, and both AzA 15% gel and 20% cream have been found to be equally efficacious in the treatment of PPR.<sup>9</sup> AzA 15% gel was superior to vehicle with statistically significant improvement in erythema and inflammatory lesions without significant side effects in another controlled study.<sup>10</sup> AzA 15% gel applied twice daily was more effective than either its vehicle or metronidazole 0.75% gel in the reduction of erythema and inflammatory lesions in a comparative trial.<sup>11</sup> The patients of moderate rosacea treated with azelaic acid (15% gel) showed therapeutic benefit over patients treated with metronidazole (1% gel) in reducing the severity of erythema on overall assessment and investigator's global assessment.<sup>12,13</sup> The improvement with AzA 15% gel in the reduction of erythema as well as the inflammatory lesions was continuous over a period of 15 weeks in a study.<sup>14</sup> Mild adverse effects did not warrant discontinuation of therapy.

## 2.3 | Metronidazole

The anti-inflammatory effect of topical metronidazole in rosacea is mediated through reduced release of ROS from neutrophils. Its effectiveness in rosacea was demonstrated by Nielson in the early eighties.<sup>15</sup> Metronidazole 1% cream applied once daily showed significant reductions in erythema and inflammatory lesions.<sup>16</sup> The efficacy of once-daily dosing of metronidazole 1% and 0.75% formulations in reducing various features of rosacea was independent of strength.<sup>17</sup> The "rosacea treatment system (RTS)" comprising cleanser, metronidazole 0.75% gel, hydrating complexion corrector, and a sunscreen (SPF30) was found to be superior in efficacy and tolerability than metronidazole and standard skin care (SSC) combination.<sup>18</sup>

## 2.4 | Sodium sulfacetamide/sulfur

Sodium sulfacetamide 10% and sulfur 5% combination has been used as a safe and effective treatment option in rosacea for a long time. As with AzA and metronidazole, it also exerts its effects through

its anti-inflammatory action.<sup>7</sup> It is contraindicated in patients with renal disease and known drug hypersensitivity. The sodium sulfacetamide/sulfur combination used for over 8 weeks achieved significant improvement in erythema, inflammatory lesions, and overall severity ratings with few and mild adverse reactions as compared to metronidazole 0.75% gel group in a trial of 63 patients.<sup>19</sup> Sodium sulfacetamide 10%/sulfur 5% cleanser, alone or in combination with topical metronidazole 0.75%, appears to be effective in patients with moderate rosacea. However, the combination therapy is superior to cleanser monotherapy in reducing papules and overall severity of the disease.<sup>20</sup> Newer wash-off formulations offer the advantages of easy incorporation in the combination, better absorption and less lasting odor and irritation.

## 2.5 | Brimonidine tartrate gel

Brimonidine tartrate, an  $\alpha$ -adrenergic receptor agonist ( $\alpha$ 2:  $\alpha$ 1 activity = 1000:1). It shows anti-inflammatory effects by vasoconstriction of very small subcutaneous vessels that results in edema inhibition. Brimonidine tartrate 0.5% gel is effective and safe in phase II and III studies conducted for the treatment of rosacea and has been the first FDA-approved therapy with improvement in the flushing and persistent erythema.<sup>21–24</sup> Significant improvement in both the clinician's erythema assessment and patient's self-assessment scores was observed with brimonidine gel 0.5% in patients of ETR after 1 month of the therapy in two multicentric, randomized trials.<sup>21</sup> Brimonidine tartrate has a faster onset of action, with most patients showing a one-grade improvement within half an hour of its application.<sup>22</sup> It can be safely used concurrently with other anti-inflammatory medications.<sup>21,23</sup> Transient worsening of erythema in a few cases (approximately after 12 h) may occur which has been attributed to an atypical pattern of vascular reactivity and response.<sup>24</sup> Allergic contact dermatitis may also occur in patients on long-term treatment.<sup>23</sup> Most adverse reactions are not associated with long-term sequelae and occur in the early phase of therapy; therefore, they do not necessitate discontinuation of medication.

## 2.6 | Oxymetazoline hydrochloride

Oxymetazoline hydrochloride (1% cream), a potent  $\alpha$ -1 agonist, has been approved by the US-FDA for the treatment of persistent erythema of rosacea. The onset of action usually occurs within 1–3 h after application, with effect lasting up to 8–10 h. A 4-week, randomized, controlled phase II trial of oxymetazoline has demonstrated 1% formulation to be the appropriate dosage as compared to 0.5% and 1% in patients with moderate-to-severe persistent facial erythema.<sup>25</sup> Oxymetazoline 1% cream was evaluated for the treatment of persistent facial erythema of rosacea versus vehicle in two randomized, controlled, phase III trials ( $N = 885$ ).<sup>26,27</sup> In both the studies, oxymetazoline 1% cream demonstrated significant superiority as compared to vehicle in reduction of erythema. An open-label

long-term (52 weeks) study in ( $N = 440$ ) also established the sustained efficacy, tolerability, and safety of oxymetazoline 1% cream applied once daily for moderate-to-severe persistent facial erythema of rosacea.<sup>28</sup>

## 2.7 | Ivermectin cream

Ivermectin is effective in the treatment of PPR. It has anti-parasitic activity against *D. folliculorum* and shows anti-inflammatory action in rosacea as it upregulates the anti-inflammatory cytokine IL-10, and inhibits pro-inflammatory cytokines such as IL-1b and TNF-alpha, and decreases neutrophilic phagocytosis and chemotaxis.<sup>29</sup> Once-a-day application of ivermectin 1% cream was more efficacious when compared to vehicle in the treatment of moderate-to-severe PPR. The investigator's assessment of rosacea severity success rate was 38.4% and 40.1% with ivermectin and 11.6% and 18.8% with vehicle, respectively, in two multicentric controlled studies.<sup>29,30</sup> Subjects in the treatment group showed increased efficacy after continued therapy up to 52 weeks. The subjects in control group were switched to AzA15% gel for twice a day application. Itching, burning, or dryness were more frequent with AzA gel compared with ivermectin cream. Once-daily use of ivermectin 1% cream was also superior to metronidazole 0.75% cream applied twice daily in reducing inflammatory lesions in rosacea.<sup>31</sup> Oral ivermectin is also found to be effective in recalcitrant oculo-cutaneous rosacea in recalcitrant PPR and in a patient with *D. folliculorum* colonization.

## 2.8 | Calcineurin inhibitors

### 2.8.1 | Tacrolimus

Tacrolimus, a non-steroidal immunomodulatory agent which inhibits proliferation and activation of CD4+ T helper cells. It binds and forms a complex with cellular receptor FK506-binding protein that binds to calcineurin and prevents dephosphorylation of the nuclear factor of activated T cells and blocks transcription of cytokine network.<sup>32</sup> Steroid-induced rosacea responds well to topical tacrolimus and has shown a significant improvement within 10 days of treatment with tacrolimus 0.075% ointment applied twice daily in a case series.<sup>8,33–35</sup> Although papulopustular lesions did not improve, treatment with 0.1% tacrolimus ointment also led to significant improvement in erythema in 24 patients of ETR and PPR subtypes.<sup>36</sup>

### 2.8.2 | Pimecrolimus

Topical pimecrolimus used twice daily as monotherapy has shown beneficial effects in 12 patients with ETR and PPR treated for 12–18 weeks in an open-label study.<sup>37</sup> Ten patients showed marked improvement, and five patients of PPR achieved  $\geq 80\%$  reduction in lesional count. Pimecrolimus has also shown great results in patients

with corticosteroid-induced rosacea after  $\leq 4$  weeks of treatment in few smaller series of patients.<sup>38,39</sup>

## 2.9 | Miscellaneous

Other topical therapies used for acne vulgaris have also been tried in the treatment of PPR. These include retinoids like adapalene and tretinoin, but are usually avoided due to their irritant potential.<sup>8</sup> Clindamycin and benzoyl peroxide in cream/gel have also been tried but have limited evidence of efficacy. The efficacy of topical vitamin C has also been shown in a small study.<sup>2</sup>

## 3 | ORAL THERAPY

Tetracyclines, macrolides, metronidazole, and isotretinoin as first-line agents have been in use since long, mainly for papulopustular, and sometimes phymatous types of rosacea.

### 3.1 | Tetracyclines

The clinical effectiveness of tetracyclines in the treatment of rosacea has been mainly attributed to their anti-inflammatory action, inhibitory effects on angiogenesis, leukocytic chemotaxis, inflammatory cytokines, and matrix metalloproteinases. Tetracycline (250–1000 mg/day), doxycycline (100–200 mg/day or 40 mg once daily of modified-release formulation), and minocycline (100–200 mg/day) are effective options for the treatment of PPR.<sup>40</sup> Minocycline and doxycycline offer the advantages of increased bioavailability, longer half-life, and minimal gastrointestinal side effects when compared to earlier, first-generation molecules.

Modified-release doxycycline (40 mg/day; 30 mg immediate-release and 10 mg delayed-release) has been approved by the FDA for the treatment of PPR.<sup>40</sup> It is as effective as standard dose of 100 mg in the treatment of rosacea with improvement of inflammatory lesions, quality of life, and provide effective and tolerable therapy without causing bacterial resistance and candidiasis.<sup>41</sup> The effectiveness and safety of up to 16 weeks therapy have been documented in PPR in two multicentric trials.<sup>42</sup> Ocular rosacea also responds well to the long-term therapy with lower-dose doxycycline.<sup>43</sup> The efficacy and safety of doxycycline is not affected by the Fitzpatrick skin type.<sup>44</sup>

Combination of oral modified-release doxycycline (40 mg once/day) and AzA 15% or metronidazole 1% gel is also effective, safe, and well-tolerated treatment for papulopustular rosacea.<sup>45</sup> Early results and better treatment outcomes are observed with AzA-based regimen than with the metronidazole-based regimen. Excellent results and long-term outcome were observed following treatment with combination of twice-daily doxycycline (100 mg/day) and AzA (15%) gel given for 12 weeks and followed by maintenance therapy with AzA gel for another 24 weeks in moderate-to-severe PPR.<sup>46</sup> Combination of modified-release doxycycline 40 mg

once-daily and topical metronidazole gel 1% reduced inflammatory lesions in mild-to-moderate rosacea earliest at 4 weeks and through 12 weeks more effectively than topical metronidazole 1% gel alone.<sup>47</sup> Recently, low-dose extended-release oral minocycline (45mg) alone as well in combination with AzA 15% gel was also found effective in PPR.<sup>48</sup>

### 3.2 | Macrolides

Macrolides like erythromycin, azithromycin, and clarithromycin have been used effectively and safely in the treatment of PPR especially in patients who are not good candidates for tetracyclines. Azithromycin and clarithromycin show faster onset of action, lesser gastrointestinal adverse effects, and better tolerability than conventional macrolides.<sup>1</sup> The safety and efficacy of azithromycin and clarithromycin in the treatment of PPR has been documented in many studies.<sup>49,50</sup> A reduction of up to 75% in total scores and an 89% in inflammatory lesion scores occurred with oral azithromycin given for 12 weeks in decreasing doses in 18 patients. Clarithromycin resulted in earlier and better outcomes than doxycycline (200 mg/day) in a comparative study.<sup>49</sup> Azithromycin is particularly useful in patients with tetracycline allergy or intolerance.<sup>51</sup>

### 3.3 | Isotretinoin

Isotretinoin (0.5–1 mg/kg/day) is primarily used to treat refractory and nodulocystic acne but can also be used effectively to treat ETR and PPR recalcitrant to other treatments.<sup>52</sup> Erythema and inflammatory lesions have responded well to oral isotretinoin 10 mg/day given up to four months in refractory PPR.<sup>53</sup> A significant improvement occurred with oral isotretinoin taken for longer periods in granulomatous rosacea of perioral skin and rhinophyma in pre-fibrotic stage.<sup>52</sup> Isotretinoin, 0.3 mg/kg/day taken for 12 weeks, maintained its superior efficacy and safety over placebo and doxycycline in a multicentric double-blinded, randomized study of 573 patients with PPR and phymatous rosacea.<sup>54</sup> The dose of 0.3 mg/kg/day was most effective and well tolerated as compared to 0.1 mg or 0.5 mg/kg/day or doxycycline 100 mg/day given for initial 2 weeks followed by 50 mg/day. Although oral antibiotics show faster therapeutic effects than the isotretinoin, their adverse effects associated with long-term use make them a sub-option in recalcitrant rosacea.<sup>55</sup> Continuous isotretinoin therapy in a “microdose (0.04–0.11 mg/kg/day)” can be an alternative in such cases provided regular laboratory monitoring and adequate contraceptive measures in child bearing women can be ensured.<sup>55</sup>

### 3.4 | Metronidazole

Oral metronidazole is effective in a set of patients with rosacea, particularly in decreasing the inflammatory lesions in PPR. Oral

metronidazole 200 mg/day administered for 6 weeks significantly reduced papulo-pustules in 29 patients with PPR.<sup>31</sup> Metronidazole (200 mg twice daily) was as effective as oxytetracycline (250 mg twice daily) in improving rosacea as early as week 6 and after 12 weeks of therapy.<sup>56</sup>

### 3.5 | Zinc

The safety and efficacy of oral zinc sulfate in the treatment of some patients with rosacea in an earlier study could not be confirmed in a double-blinded, placebo-controlled study of 44 patients with moderate-to-severe rosacea treated with oral zinc sulfate 220 mg twice a day for 90 days.<sup>57</sup>

### 3.6 | Miscellaneous

Various vasoactive compounds have also been tried for the treatment of rosacea-associated symptoms. A quick and substantial improvement in persistent erythema and flushing with no untoward side effects was seen in two female patients of rosacea treated with oral ondansetron 8 mg twice daily for 1 week and 4 mg twice daily thereafter.<sup>58</sup> Propranolol, nadolol, clonidine hydrochloride, naloxone acetyl salicylic acid, oral contraceptives, spironolactone, and selective serotonin reuptake inhibitors have also been used, but more evidence for their efficacy is needed to make any recommendation.<sup>7</sup>

## 4 | LASERS AND LIGHT THERAPY

Light therapies and lasers have been effectively used over the years for the management of rosacea. These include the intense pulsed light (IPL, 500–1200 nm), pulsed dye laser (PDL, 585–595 nm), potassium titanyl phosphate (KTP, 532 nm) laser, and long-pulsed neodymium:yttrium-aluminum-garnet laser (Nd:YAG, 1064 nm). In addition, ablative lasers like carbon dioxide (CO<sub>2</sub>) and erbium:yttrium-aluminum-garnet (Er:YAG) lasers are of use in the treatment of phymatous rosacea. Light-based therapies are particularly effective in treating the varied vascular manifestations of the disease viz. flushing, erythema, and telangiectasia. Both long-pulsed dye lasers and intense pulsed light devices are an effective modality for the treatment of the disease and are associated with significant patient satisfaction, especially as the vascular component may not improve with other therapies.

### 4.1 | Intense pulsed light

Intense pulsed light is effective as a monotherapy as well as in combination with other modalities for the treatment of erythematotelangiectatic and phymatous rosacea. Its role in the treatment of flushing, telangiectasia, and persistent erythema has been

successfully demonstrated over the years. It produces a non-coherent beam of light with wavelengths ranging from 500 to 1200 nm by using cut-off filters from 515, 550, 560, 570, and 590 nm for vascular lesions. The clinical efficacy of the device can be improved by using the longer wavelengths which penetrate deeper into tissue. Cooling of the skin can be achieved by splitting the energy into two or three pulses with different pulse delays.

Angermeier reported 75%–100% clearance with 4 IPL sessions with minimal side effects in 200 patients with rosacea, primary telangiectasia, facial hemangiomas, and port wine stains.<sup>59</sup> A 30% decrease in blood flow, 21% decrease in the erythema, and 29% decrease in the telangiectatic area occurred in four patients treated for rosacea with IPL at 3-week intervals for 5 sessions in another study.<sup>60</sup> In a similar study of 32 patients, 83% of patients showed reduction in redness, 75% decreased flushing and improved skin texture, and 64% reported fewer acneiform lesions after 1–7 IPL sessions.<sup>61</sup> Schroeter treated 508 sites in 60 patients, with a mean of 4.1 treatments, and demonstrated 77.8% mean clearance that was maintained in the follow-up months, with negligible adverse effects.<sup>62</sup> Combination of pulsed light therapies and bipolar radiofrequency is another treatment option for patients not responding to medical therapy or are not suitable candidates for it. A significant improvement was noted in both erythema and telangiectasia in 21 patients with ETR by using electro-optical synergy device (ELOS).<sup>63</sup> Papageorgiou and colleagues treated 34 patients with a 560-nm filter in 4 sessions performed at 3-week intervals and observed nearly 39% reduction in erythema on the cheeks and 22% on the chin, respectively. The photographic improvement in erythema and telangiectasia was 46% and 55%, respectively. The results were sustained at 6 months with minimal side effects.<sup>64</sup> More than hundred patients of varied rosacea severity were treated at 1–3-week intervals by various parameters using the IPL with a 530-nm filter. Eighty percent of patients showed a reduction in redness, 78% reported improvement in flushing, and 72% fewer acneiform breakouts.<sup>65</sup>

### 4.2 | Pulsed dye laser

Pulsed dye laser (PDL) improves both the clinical signs and symptoms of rosacea. It emits light in the wavelength of 585–595 nm corresponding with the absorption peak of oxyhemoglobin targeting the superficial vessels. Significant improvement is observed in symptoms and signs like erythema, and quality-of-life scores in patients of ETR with PDL systems at purpuragenic fluences.<sup>66</sup> Thicker and denser telangiectasia benefit more from purpuragenic treatment than finer and sparser telangiectasia. In a study of 11 patients treated with variable pulse, PDL demonstrated reduction in telangiectasia ratings from 2.7 to 2.4 after 6 weeks with a single treatment at purpura-free lower fluences. Purpuragenic treatments resulted in further decrease to 1.4 from the baseline.<sup>67</sup> However, the adverse effect of post-treatment purpura and dyspigmentation seen with earlier device systems can be decreased by specifically targeting telangiectasias using longer pulse durations.<sup>67,68</sup> Long-pulsed (595 nm) PDL at sub-purpuric fluences was used to treat rosacea-associated

telangiectasia in 12 patients in one study.<sup>69</sup> Two patients each showed more than 75% and 50% to 75% improvement while 5 patients 25%–50% improvement.

Pulsed dye laser also appears equally effective in reducing rosacea-related symptoms and signs when compared to IPL in a controlled study comparing the both.<sup>70</sup> PDL (non-purpuragenic fluences: 7 J/cm<sup>2</sup>, 10-mm spot size, 6-ms pulse duration) and IPL (560-nm filter, pulse train: 2.4 and 6.0 ms, pulse delay: 15ms, fluence: 25 J/cm<sup>2</sup>) achieved significant and similar reduction in erythema, telangiectasia, and other symptoms compared with controls. PDL can also be used in ELOS to treat moderate-to-severe ETR.<sup>63</sup> Similarly, telangiectasia respond fairly well to both, the flashlamp-pumped long-PDL (590–595 nm) and the KTP laser (532 nm), with PDL resulting in better treatment outcomes.<sup>71</sup> A substantial decrease in the cutaneous substance P levels has been demonstrated in patients with ETR after treatment with PDL and neodymium:yttrium-aluminum-garnet (Nd:YAG) laser treatment in a split-face study.<sup>72</sup> PDL decreased facial erythema by 6.4% more spectrophotometric levels (8.9% vs. 2.5%) from baseline than Nd:YAG (1064 nm) in another split-face study comprising 14 patients.<sup>73</sup> Patients' self-assessment of the redness also showed significant improvement with both.

### 4.3 | Potassium titanyl phosphate (KTP) laser

Potassium titanyl phosphate laser is quite effective in the treatment of telangiectasia in patients of rosacea. KTP laser interacts with superficial chromophores, making it useful for various superficial vascular lesions. It emits 532-nm green light which is produced by passing Nd:YAG light through a KTP crystal that halves its wavelength.<sup>74-76</sup> Though it usually targets the superficial vessels causing minimal discomfort and post-inflammatory hyperpigmentation, wider pulse widths can be used for the treatment of larger vessels in Fitzpatrick skin types I-IV.<sup>74</sup>

Nearly 77% patients with various vascular lesions including a significant number of discrete telangiectasias (33.7%) showed either clearance or marked improvement after 6 weeks of treatment.<sup>75</sup> Comparative studies of KTP laser and PDL have demonstrated effectiveness of the KTP laser in reduction of facial telangiectasia.<sup>71</sup> Although the PDL was found to be better than the KTP laser in the reduction of telangiectasia, the latter resulted in lesser pain, dyspigmentation, and purpura. KTP laser resulted in similar improvements in clinical features as IPL but it also caused a significant rise in the skin temperature. Almost 90% of facial telangiectasia showed marked improvement with KTP laser in 204 patients (with various superficial cutaneous vascular lesions) in a two-year retrospective analysis.<sup>76</sup>

### 4.4 | Neodymium:Yttrium-aluminum-garnet laser

Although not often used in the treatment of rosacea, Nd:YAG laser (1064 nm) appears to be safe and effective treatment for ETR as demonstrated in the two separate split-face trials.<sup>73</sup> Large deep

cutaneous vessels with bluish hue particularly seem to respond well to long-pulsed Nd:YAG laser.

### 4.5 | Diode lasers

Diode laser (890–980 nm) has also been used successfully to treat telangiectasias in rosacea patients.<sup>77</sup> Different tissue effects can be generated by using different laser parameters. Facial telangiectasias and couperose warrant several sessions to obtain satisfying results with nasal telangiectasias being particularly painful. The pulse duration should be at least three times shorter than pulse pause to avoid ulcerations.

### 4.6 | Ablative lasers

The ablative lasers are of particular benefit as they provide a dry surgical field, which helps in proper contouring of deformed areas, resulting in tremendous cosmetic results in few treatment sessions. CO<sub>2</sub> laser (10 600 nm) and erbium:yttrium-aluminum-garnet (Er:YAG, 2940 nm) are used for ablation in phymatous rosacea especially rhinophyma to correct the shape of deformed nose.<sup>66</sup> Sequential combination of CO<sub>2</sub> laser with PDL has also been used successfully to treat a rapidly progressing rhinophyma in a middle-aged Caucasian man.<sup>78</sup> Post-treatment erythema, swelling, and crusting can delay healing, and patients need to be counseled for the risk of scarring and permanent dyspigmentation.

## 5 | OTHER SURGICAL MODALITIES

Phymatous rosacea presents a difficult-to-treat preposition to the clinicians. It usually occurs alone but can also present along with other subtypes. Even occurrence of rhinophyma with otophyma simultaneously in a female patient has also been seen.<sup>79</sup> Surgical excision is one of the alternatives for the treatment of rhinophyma. Excision with razor blades and tangential excisions using scalpel in either local or general anesthesia in the hands of experienced physicians have borne satisfactory results.<sup>80</sup> Radiofrequency ablation is very effective in the treatment of rhinophyma, and because it causes less heat in the tissue than lasers and electrosurgery, it has a better safety profile when used judiciously. Other methods like dermabrasion, electrosurgery, bipolar electrocoagulation, ultrasonic scalpel, hydrojet excision, carbon dioxide laser vaporization, and cryotherapy have all been tried to correct rhinophyma with variable results.<sup>8,80</sup> Most of these options are associated with substantial risk of scarring.

### 5.1 | Botulinum toxin

Botulinum toxin (BTX) as an intradermal injection has been used as an off-label treatment for reducing erythema and flushing in rosacea.

BTX blocks the release of acetylcholine from peripheral autonomic nerve endings of cutaneous vessels, thereby reducing the flushing. It also inhibits the release of substance P and calcitonin gene-related peptide, thence leading to reduced skin inflammation.

The therapeutic effect of BTX was compared with placebo (saline solution) in one of the initial randomized controlled trial.<sup>81</sup> A small set of patients ( $N = 15$ ) treated with a single injection of BTX (15–45 IU) on face demonstrated statistically significant improvement in erythema, as compared to baseline.<sup>82</sup> Various researchers who used different amounts of BTX (ranging from 1 to 6 IU/cm<sup>2</sup>) intradermal injections and variable frequency of treatments (1–3 sessions with different intervals) have all yielded positive results.<sup>81–84</sup>

## 6 | SKIN CARE AND PATIENT EDUCATION

Patient education about rosacea and its triggers is crucial in a comprehensive management. However, there is no uniformity of aggravating factors. Patients of rosacea have sensitive skin which flushes readily on exposure to sunlight or heat, alcohol consumption, and hot spicy foods. An individualized approach with regard to avoidance of trigger factors is needed, and patients should be counseled about photoprotection. It is recommended that rosacea patients routinely use a high-SPF broad-spectrum sunscreen. Patients should be advised that, as UVA can penetrate through clouds and glass shield, the sunscreen should be worn daily all year round. Physical sunscreens containing zinc oxide, titanium dioxide, silicones like dimethicone or cyclomethicone should be preferred. Adequate skin care by using mild soap-free cleansers and use of emollients and humectant moisturizing agent helps greatly in reducing skin irritation and maintaining the epidermal barrier function. Heavy foundations, sodium lauryl sulfate-containing products, astringents, toners, menthols, and water-proof cosmetics should be avoided.

## 7 | CONCLUSION

The opening of different domains in the molecular pathogenesis of rosacea has led to the emergence of newer interventions. The addition of new formulations like topical brimonidine and oxymetazoline, oral therapies in the form of modified-release doxycycline, ondansetron, etc. and new light/laser devices has increased our therapeutic armamentarium. Based on newer research on pathophysiology, newer molecules are being tested and tried to answer the challenges in the treatment of rosacea.

### CONFLICT OF INTEREST

None.

### ETHICAL APPROVAL

No ethical approval was required as this research did not involve human subjects or animals.

### AUTHOR CONTRIBUTIONS

Anuj Sharma involved in writing and revising the manuscript. George Kroumpouzou, Martin Kassir, Hassan Galadari, Andy Goren, and Stephan Grabbe contributed to review and revising the manuscript. Mohamad Goldust contributed to conception, writing, review, and revising the manuscript.

### DISCLAIMER

“We confirm that the manuscript has been read and approved by all the authors that the requirements for authorship as stated earlier in this document have been met and that each author believes that the manuscript represents honest work.”

### DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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