




Conventional and Novel Treatment Modalities in Rosacea

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Abstract: Rosacea is a common skin disease that is troublesome for both the patients and the dermatologists. Erythema, telangiectasia, papulopustular changes and phymatous changes are the main problems faced by the patients and dermatologists in everyday practice. Due to the chronic and relapsing nature of the disease, patients are usually unsatisfied with conventional treatment methods. This article aims at redefining rosacea according to the 2017 consensus and reviewing the different treatment modalities for different manifestations of the disease in depth.

Keywords: new, resistant, rosacea, treatment

Introduction

Rosacea is a chronic inflammatory skin disease of complex pathogenesis. It mainly affects the central face.^{1,2} The disease has no gender preference. It may be seen at any age; however, the typical onset is after 30 years of age.³ The disease course typically shows remissions and exacerbations. In fair-skinned individuals the disease has a prevalence of up to 10%. Yet, the disease is not limited to fair skin; it may be seen in skin of color as well.⁴

The clinical presentation of the disease includes facial erythema (transient or persistent), telangiectasia, edema, papules and pustules. The patient may present with either one or a combination of these. The patients can be asymptomatic or complain of burning, stinging, pain or pruritus.²

Initially, the disease was classified into 4 main subtypes. These were erythematotelangiectatic (subtype 1), papulopustular (subtype 2), phymatous (subtype 3) and ocular (subtype 4). Granulomatous rosacea was considered as a variant of rosacea rather than a subtype.³ However, not only a subtype may progress into another but also these subtypes may occur simultaneously. Therefore, in 2017, there was a shift from subtypes to phenotypes in the diagnosis of rosacea and at least one diagnostic or two major phenotypes are required in order to diagnose a patient with rosacea.⁴ These phenotypes are summarized in Table 1.^{4,5}

The diagnostic phenotypes are^{4,5}

- Persistent erythema of the central face that exacerbates with triggering factors
- Phymatous changes (most commonly rhinophyma)

The major phenotypes are^{4,5}

- Transient facial erythema of the central face/flushing

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Table 1 Phenotypes According to the 2017 Consensus^{4,5}

Diagnostic Phenotypes	Major Phenotypes	Minor Phenotypes
Persistent facial erythema	Transient facial erythema	Burning
Phymatous changes	Inflammatory papules and pustules	Stinging
	Telangiectasia	Edema
	Ocular changes	Dryness

- Inflammatory papules and pustules
- Telangiectasia
- Ocular changes: blepharitis, keratitis, conjunctivitis, telangiectasia of lid margins

The minor phenotypes are^{4,5}

- Burning
- Stinging
- Edema
- Dryness

As rosacea is a disease of complex pathogenesis and a spectrum of presentations, its treatment possesses a challenge for the dermatologists. In the following sections the major treatment challenges in erythema, flushing, telangiectasia, inflammatory lesions and phymatous changes will be addressed and possible solutions will be reviewed.

Flushing, Transient and Persistent Erythema

Transient or persistent facial erythema is the most common presenting feature in rosacea patients of all subtypes. It's a very common clinical challenge faced by the dermatologists in the everyday practice.⁶ Rosacea symptoms often start with flushing and leads to persistent erythema.⁷ Facial erythema is usually diffuse in distribution and is located on the central portion of the face. Although inflammatory lesions may subside with time, erythema has a propensity to persist. Increased innate immunity, neurovascular and neuro-immune dysregulation have a central role in the development and persistence of facial erythema via vasodilation.⁸

Currently available treatment modalities in rosacea are directed more towards inflammatory changes than erythema; these are: topical metronidazole, topical azelaic acid and systemic tetracyclines. Although in theory,

topical metronidazole and topical azelaic acid should treat erythema on molecular basis, current studies show these usually fail in the treatment of erythema, especially if it has become persistent.⁸

It is a therapeutic challenge for dermatologists that there are a limited number of effective topical agents that can be used in the treatment of diffuse facial erythema of rosacea patients. Of these a very commonly used one is topical steroids. However, with the use of topical steroids cutaneous atrophy is inevitable and flare-ups are seen as the therapy is ceased. For those reasons, the use of topical corticosteroids should be avoided in rosacea patients.^{6,9} Topical calcineurin inhibitors may be of benefit in decreasing the facial erythema in certain cases, however, they do exacerbate rosacea most of the time.^{6,10,11}

Lasers are increasingly used modalities in the treatment of vascular lesions. 595 nm Pulse-dye laser (PDL) is a well-accepted modality in the treatment of diffuse facial erythema. PDL treatment in purpuragenic doses usually produces sufficient cosmetic improvement in 2 treatment sessions. Furthermore, it decreases burning, stinging, sensitivity, itching and dryness; thus increases the quality of life of the patient dramatically. However, patient discomfort and facial bruising secondary to the procedure withholds the use of PDL at purpuragenic doses.¹² PDL is effective in reducing facial erythema in sub-purpuragenic doses as well, but an increased number of treatment sessions is required.^{12,13} Recently, intense pulsed light (IPL) which is a flashlight that emits non-coherent light of wavelength between 400–1400 nm, was compared to PDL (at non-purpuragenic doses) in the treatment of diffuse facial erythema. Not only was IPL, when filtered at 560 nm, found to be as effective as PDL in the treatment of facial erythema, but also the patients treated with IPL demonstrated greater improvement than those treated with PDL in the 90 days follow-up. Furthermore, it did not produce any major side effects.¹³ Thus, in patients with persistent diffuse facial erythema; both PDL and IPL may be used for cosmetic improvement.

Brimonidine tartrate 0.5% gel is a topical agent that was approved for the treatment of transient and persistent facial erythema in rosacea patients older than 18 years.^{14,15} It is a potent vasoconstrictor that binds selectively to the alpha-2 adrenergic receptors on vascular smooth muscle cells of peripheral cutaneous vasculature.¹⁴ Patients treated with topical brimonidine clinically show 60–70% reduction in erythema with minimal side effects. Furthermore, its effect starts as early as in 30 mins.¹⁶ However,

a handicap in its use is that the effect of brimonidine gel is transient; erythema reappears within 9–12 hrs. Therefore, once daily use may not be sufficient and twice daily use may be necessary.^{6,16} However, an important point to address is that worsening of erythema can be seen due to brimonidine use. This side-effect can be overcome with the proper use of barrier creams and avoiding the overuse of brimonidine.¹⁷

Another novel topical agent that was approved recently for the treatment of facial erythema is oxymetazoline hydrochloride 1% cream.¹⁵ It is an alpha-1a adrenergic receptor agonist that is used in the treatment of moderate to severe persistent facial erythema in rosacea patients.¹⁸ At higher concentrations it binds to alpha-2 adrenergic receptors as well.¹⁵ Baumann et al followed patients with facial erythema applying oxymetazoline cream for 29 days and concluded that topical oxymetazoline is a safe and effective treatment modality for moderate to severe facial erythema when applied once daily.¹⁸ Tanghetti et al have demonstrated that oxymetazoline is effective in reducing facial erythema starting at one hour following its initial application.¹⁹ Thus, oxymetazoline cream is an effective and easy-to-use topical alternative in the treatment of resistant facial erythema with its once daily application regimen.

In addition to topical antihypertensive drugs, systemic antihypertensive drugs are used off-label in the treatment of facial erythema.⁶ Beta blockers can be used in the treatment of refractory facial erythema. Nadolol and propranolol, which are non-selective beta adrenergic antagonists, are effective at reducing flushing. However, their uses were abandoned due to their possible side effects: hypotension and bradycardia. Carvedilol, a non-selective beta adrenergic and an alpha-1 antagonist, is a better alternative in the treatment of refractory facial erythema. When used as 3.125–6.25 mg, 2 to 3 times daily, carvedilol leads to clinical improvement in 3 weeks without the side effects of nadolol and propranolol. Carvedilol differs from other non-selective beta-adrenergic blockers in that its metabolites are potent antioxidants. This feature further enhances its therapeutic efficacy in facial erythema.²⁰ On the other hand; the use of calcium channel blockers in the treatment of facial erythema is not recommended because they may exacerbate rosacea.⁶ Clonidine is a centrally acting antihypertensive that works via alpha-two adrenergic agonistic activity. Wilkin investigated the use of systemic clonidine hydrochloride in the treatment of flushing. The patients were given 0.05 mg clonidine hydrochloride twice daily

for two weeks. Although clonidine did not produce a major alteration in arterial blood pressure, it did not reduce flushing provoked by red wine, chocolate and hot weather, as well.²¹ Cunliffe et al also investigated the effect of clonidine on flushing. Likewise, 0.05 mg clonidine hydrochloride was administered to patients twice daily. Similar to Wilkin's findings, clonidine was found to be not beneficial in suppressing flushing attacks.²²

Intradermal botulinum toxin type-A (Botox) injection is a promising treatment modality for facial flushing and erythema. The release of acetylcholine leads to vasodilation of cutaneous vessels which presents as flushing and facial erythema. Botox interferes with the release of acetylcholine and provides symptomatic relief for the patients with flushing and facial erythema.²³ Park et al have reported two patients whose erythema were successfully treated with Botox injections. The first patient received a total dose of 50 units and the second patient received a total dose of 65 units. Each patient received the total dose within two treatment sessions and appreciable cosmetic results were achieved one week after the second treatment session in both cases. Symptomatic relief was persistent for 4 months in both cases and patients applied to the clinic for the second course of treatment.²⁴ Bloom et al have conducted a study of 15 patients with facial erythema, each patient receiving 15–45 units of intradermal botox injection. They have concluded that intradermal botox injection is an effective and safe treatment modality for facial erythema of rosacea.²⁵ In short, intradermal botox injections were shown to help relieve facial erythema in several rosacea patients; further studies with larger sample sizes can be conducted to exemplify this treatment modality in depth.

Telangiectasia

Telangiectasias are cosmetically disturbing for the patients and they often seek treatment. Nevertheless, topical or systemic agents are ineffective in the treatment of telangiectasia. Physical modalities, ie laser and light based devices are currently used in the treatment of vascular manifestations of rosacea. An average of one to four sessions is required for cosmetically acceptable results.²⁶ The basis of these therapies is that hemoglobin absorbs the energy emitted by these devices which leads to the disappearance of vascular lesions.²⁴ Neodymium-doped, yttrium-aluminum-garnet (Nd-YAG) laser, 532 nm Potassium-Titanil-Phosphate (KTP), 595 nm PDL, IPL and dual wavelength long-pulsed 775 nm alexandrite/1,064 nm neodymium:

yttrium-aluminum (LPAN) are examples of these modalities.^{26,27}

The most widely accepted examples of these are PDL, Nd:YAG and IPL. In a review article by Anzegruber et al, it was concluded that IPL was recommended at level A and Nd:YAG laser (including KTP) and PDL were recommended at level B. Due to its larger spot size, IPL produces fewer side effects compared to PDL; therefore its use is more advantageous compared to PDL. Furthermore, PDL is more effective than Nd:YAG in the treatment of vascular manifestations, however, Nd:YAG produces less pain.²⁶ The effectiveness of Nd:YAG lasers in the treatment of erythema, telangiectasia and skin texture of rosacea patients can be increased by combining it with topical retinoic acid preparations. Blind evaluators assessed that topical retinoic acids increased the treatment response to Nd:YAG laser by 47%.²⁸

Radiofrequency (RF) devices induce focal damage within the dermis by producing heat and electric current via electromagnetic radiation. This damage stimulates new collagen formation through a rapid healing process. Compared to laser treatments, RF is a newer treatment modality for rosacea. A study by Kim et al compared the treatment efficacy of RF and PDL in rosacea. Both modalities were applied for 3 sessions with monthly intervals. RF and PDL produced similar results in the treatment of erythematotelangiectatic rosacea; there was no statistically significant difference. Thus, both RF and PDL are effective in the treatment of erythema and telangiectasia. On the other hand, RF was more efficacious than PDL in patients suffering from papulopustular telangiectasia.²⁹ In a study of 21 patients with moderate-to-severe rosacea, PDL was combined with RF. It was concluded that the combination therapy was more efficacious than PDL alone in the treatment of erythema, flushing and telangiectasia.²⁶ Therefore, in the treatment of resistant erythematotelangiectatic rosacea, PDL and RF can be considered for treatment alone or in combination.

Newly emerging combination therapies are found to be more effective in the treatment of resistant rosacea patients than single modality therapies. The addition of PDL treatment to oral minocycline therapy was found to decrease the relapse rates in patients suffering from erythema and telangiectasia. The recurrence rate of minocycline alone was 48%; however the recurrence rate of minocycline combined with PDL was 37%.³⁰ Furthermore, Nd:YAG laser treatment can be added to topical brimonidine therapy. Brimonidine alone is effective in the treatment of erythema,

though this effect is transient. However, telangiectasias persist after brimonidine treatment. Cosmetically better treatment results were obtained when patients with erythematotelangiectatic rosacea were treated with Nd:YAG laser initially and topical brimonidine therapy was added 1 month afterwards.³¹

Papulopustular Lesions

Inflammatory papules and pustules are major phenotypes observed in rosacea patients.^{4,5} In mild lesions, topical treatment alone can be sufficient. On the other hand, systemic and topical treatments methods should be combined in moderate to severe cases. There are a wide variety of topical modalities used in the treatment of papulopustular rosacea (PPR); these are: metronidazole, azaleic acid, ivermectin, pimecrolimus, retinoids, permethrin, benzoyl peroxide, erythromycin and dapsone.²⁶ Nd:YAG laser, PDL and RF are also effective in the treatment of papulopustular lesions.^{26,29} The systemic treatment modalities for papulopustular lesions are oral antibiotics, oral zinc sulphate and oral ivermectin.²⁶

Metronidazole 0.75–1% cream is effective in the treatment of PPR when applied twice daily.²⁶ In a randomized controlled trial of 51 patients, topical metronidazole was found to have a clearance rate of 90%, which is similar to that of oral tetracyclines.³² A study by Dahl et al, compared the efficacy of 0.75% and 1% topical metronidazole and found no difference between the two concentrations.³³ Azaleic acid, when used topically, inhibits the production of reactive oxygen species and induces the production of pro-inflammatory cytokines.²⁶ Azaleic acid 15% gel, applied twice daily for 15 weeks produced significantly better treatment results in papules and pustules when compared to 0.75% metronidazole cream.³⁴ Azaleic acid 15% foam is also effective in the treatment of PPR when used for 12 weeks.³⁵ Furthermore, azaleic acid foam produces less side effects than azaleic acid gel when both of them are used in 15% concentration.³⁶ Thus, both metronidazole (0.75–1%) and azaleic acid (15%) are effective in the treatment of PPR when used topically.

Ivermectin is an anti-parasitic drug that decreases the demodex density of the skins of patients with rosacea. Demodex mites are normally found in human flora; however, their density is increased in patients with rosacea. Ivermectin produces its anti-inflammatory effects via its effects on these mites.²⁷ Ivermectin 1% cream, is a safe and tolerable alternative 1st line treatment for PPR.³⁷ It is more effective for the treatment of PPR than metronidazole

0.75% cream. However, its efficacy was not compared to topical azaleic acid 15%, which is also more efficacious than topical metronidazole 0.75%.³⁸ Dall'Oglio et al conducted a study investigating the efficacy of 1% ivermectin cream in the treatment of PPR. They used erythema-directed photography for the assessment of results. Thirty-two percent of the cases achieved complete resolution with 8 weeks-use of topical ivermectin. Furthermore, a significant reduction in erythema was observed.³⁹ Ivermectin is a safe and effective topical treatment alternative for refractive PPR patients and is registered in Europe and in the US.²⁶

Topical pimecrolimus 1% cream, which is a calcineurin inhibitor, is also an effective alternative in PPR treatment. It is as efficacious as 1% metronidazole cream. However, it is also a culprit drug for inducing rosacea.²⁶

Retinoids are also an alternative for the treatment of inflammatory rosacea lesions. However, it should be kept in mind that the irritant side effects of retinoids can be more pronounced in rosacea patients with gentle skin. Of retinoids, only tretinoin 0.025% and adapalene gel were tolerable and used successfully in the treatment of PPR.²⁶

Permethrin 5% cream, when applied twice daily topically for 2 months is as effective as metronidazole in the treatment of PPR. It also has a favorable side effect profile. It produces even more benefit when it is combined with other anti-inflammatory modalities.⁴⁰ Topical permethrin 5% is effective in the treatment of erythema and papules of rosacea patients, however it is ineffective for telangiectasia and pustules. Still, it is recommended as class A for the treatment of PPR.²⁶

Topical erythromycin 2% gel is as efficacious as metronidazole 0.75% cream in the treatment of PPR.²⁶ When combined with benzoyl peroxide, topical erythromycin produces better results than topical metronidazole. Thus, this combination is a good treatment alternative for acne rosacea.⁴¹ Benzoyl peroxide 5% gel combination with clarithromycin gel, is also recommended for the treatment of PPR.²⁶ Dapsone 5% gel, when used for 12 weeks, is also as effective as metronidazole 0.75% cream and thus can be used in the treatment of PPR.⁴²

As for systemic antibiotics, low dose oral tetracyclines (eg 40 mg/day doxycycline) are effective in the treatment of PPR. Azithromycin and clarithromycin are also used in the treatment of PPR. Although one randomized clinical trial found 500 mg daily azithromycin as efficacious as 100mg/day doxycycline, overall, azithromycin and clarithromycin are considered to be less effective than

doxycycline for the treatment of PPR. Ampicillin can also be tried in refractory cases. It is not as effective as oral tetracyclines though.²⁶ Although antibiotic resistance is a major concern worldwide, the daily use of 40 mg/day doxycycline was not found to be leading to antibiotic resistance even with prolonged use.^{43–45}

Retinoids, topically or systemically, are used in the treatment of rosacea because of their anti-inflammatory properties at lower doses (eg 0.3–0.5 mg/kg/day).²⁶ 20 mg/day isotretinoin is effective in reducing erythema and inflammatory lesions.⁴⁶ Oral isotretinoin not only provides rapid improvement, but it also decreases relapse rates. Compared to topical retinoids, eg Tretinoin 0.025% cream, systemic retinoids are more effective.²⁶

Zinc sulphate, when administered orally with a dose of 100 mg/day, is also effective in reducing inflammatory lesions of rosacea. It has a favorable side effect profile. The sole side effect to be reported was gastric upset in 12% of the patients.⁴⁷ Oral ivermectin (200 micrograms/kg/day) is also a treatment alternative for PPR although it is supported with level D evidence. In patients with treatment resistant rosacea, combination of oral ivermectin and permethrin 5% cream can be considered since this combination was found to be effective in decreasing demodex density in immunocompromised patients as well.²⁶

Phymatous Changes

Phymatous changes are due to the hypertrophy of sebaceous glands, proliferation of blood vessels and connective tissues. Phymata most commonly occur on the nose, especially the lower third, which is referred to as rhinophyma. Other forms of phymata are gnathophyma (jaw/chin), metophyma (forehead), blepharophyma (eyelid) and otophyma (ear). Although all of these entities have a benign course, they are problematic for the sufferers due their cosmetic and functional impairment.⁴⁸ Systemic treatment options for phymatous changes include low dose doxycycline (40 mg/day) and low dose isotretinoin (0.3 mg/kg/day). Both of these are supported by level A evidence.²⁶ Surgical modalities can also be used in the treatment of phymatous changes and in fact they are more effective. These modalities are excision, dermabrasion, electrocoagulation and laser ablation.⁴⁸

Simple excision is a widely accepted method. However, since phymatous changes have a large blood supply, excision of phymata can lead to excessive bleeding, which is an unwanted complication. Furthermore, there is the risk of removing excessive tissue. Dermabrasion can also be used

to make the skin surface smoother. However, similar to surgical excision, dermabrasion can also lead to excessive bleeding.⁴⁸

Electrocoagulation is more advantageous in terms of bleeding control compared to surgical excision. Additionally, it is a quicker method compared to simple excision. However, it withholds the risk of cartilaginous necrosis of nose due to excessive heat. Furthermore, atrophic scars and prolonged wound healing have also been reported with treatment of phymatous changes with electrocoagulation.⁴⁸

Currently used laser devices in the treatment of phymatous changes are CO₂ laser and Erbium:YAG laser. Both of these lasers have a high affinity for water, which leads to ablative changes since the skin has a high water composition.⁴¹ Madan et al evaluated the effectiveness of CO₂ laser in rhinophyma treatment. They have demonstrated that, over a three-months recovery period after single session treatment, of the 124 patients, 115 were very satisfied with the results. Furthermore, the method had a tolerable side effect profile.⁴⁹ CO₂ laser is also good

at hemostasis due to its coagulative properties.⁴⁸ Another combination therapy that can be used in rosacea treatment is Er: YAG and CO₂ laser treatment.⁵⁰ CO₂ laser is used for its coagulative properties when it is used together with Er:YAG laser.⁴⁸ Goon et al proposed that, optimal cosmetic results with minimal scarring can be obtained with this combination therapy.⁵⁰

Conclusion

Rosacea is a common and life-long disease that is troublesome for the patients. Although there are many treatment modalities for different manifestations of the disease, patients are usually unsatisfied with the results. This is a challenge for the dermatologists. There are many newly emerging treatment modalities for erythema, telangiectasias, inflammatory lesions and phymatous changes that are resistant to conventional methods. The conventional and novel treatment modalities are summarized in Table 2. Nevertheless, the relapsing nature of the disease decreases the chance of disease free survival.

Table 2 Conventional and Novel Treatment Modalities

Redness		Telangiectasia		PPR		Phymata	
Topical	Corticosteroids Calcineurin inhibitors Brimonidine gel (0.5%) Oxymetazoline hydrochloride cream (1%) Ivermectin cream (1%)	Laser and light based devices RF	Nd:YAG (1064 nm) KTP (532 nm) PDL (595 nm) LPAN (775 nm/1064 nm)	Topical	Metronidazole cream (0.75–1%) Azeleic acid gel/foam (15%) Ivermectin cream (1%) Pimecrolimus cream (1%) Retinoids (tretinoin 0.025% gel, adapalen gel)	Oral low dose doxycycline+ retinoid Excision Dermabrasion Laser ablation	CO ₂ (10,600 nm) Er:YAG (2940 nm)
Laser and light based devices	PDL (595 nm) IPL (560nm)				Permethrin cream (5%) Benzoyl peroxide gel (5%)	Electrocoagulation	
Systemic antihypertensives	Carvedilol Clonidine				Erythromycin gel (2%) Dapsone gel (2%)		
Intradermal botox				Laser and light based devices RF Oral antibiotics Zinc sulphate Oral ivermectin	Nd:YAG (1064 nm) PDL (595 nm)		

Disclosure

The authors report no conflicts of interest in this work.

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