Rosacea Roadmap
The Route to Management Success

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Rosacea Treatment Overview

Introduction

Rosacea is a commonly observed dermatologic condition that affects a vast number of persons, causing significant physical and emotional distress. Appearing generally between the third and fifth decade of life, rosacea occurs mostly in Caucasians of northern European descent. Rosacea has an incidence of about 1 in 20 (13 million) Americans. Although rosacea appears to affect women 2-3 times more often than men, women are less likely to develop phymatous changes. Considered by some to be a syndrome rather than a disease, rosacea is characterized by exacerbations of centrofacial (forehead, nose, cheeks, chin) erythema and flushing, which may be accompanied by papules, pustules, and telangiectasia (dilated superficial blood vessels). In some patients, diffuse hyperplasia of connective tissue and sebaceous glands may occur, causing a bulbous proliferation of the nose, or rhinophyma, which is particularly severe and disfiguring. As noted above, rhinophyma occurs more often in men. Rosacea may also present in an ocular form as conjunctivitis, with or without blepharitis, and in more severe cases as keratitis.

The precise etiology of rosacea remains unknown, and numerous factors have been proposed that may contribute to its origin. A variety of treatment approaches are available to manage this chronic disorder, punctuated by periods of exacerbation and remission. Although rosacea is incurable, its clinical signs and symptoms can be controlled and even halted through medical therapy and lifestyle modification.

Classification of Rosacea

In an attempt to establish a more precise reference tool for rosacea, a committee of the National Rosacea Society recently developed a classification system, which provides standard criteria for diagnostic and research purposes, as well as standard terminology for practitioners, payors, and patients. This classification system incorporates primary and secondary diagnostic criteria, four descriptive subtypes, and one variant (Table 1).

The classification of rosacea as various subtypes reflects that it is not typically a progressive disease. Many persons with rosacea may experience fluctuating signs of erythema with or without inflammatory lesions, or erythema with telangiectases, and never develop ocular lesions or rhinophymas. Each subtype includes the fewest signs sufficient to make a diagnosis of the subtype, and it is not uncommon for patients to have characteristics of more than one subtype simultaneously.
Table 1. Subtypes and Variants of Rosacea

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subtype 1: Erythematotelangiectatic Rosacea</td>
<td>Flushing, central erythema, Telangiectasia, stinging, burning, roughness, scaling may also be present.</td>
</tr>
<tr>
<td>Subtype 2: Papulopustular Rosacea</td>
<td>Persistent central facial erythema; papules, pustules. Telangiectasia may be present.</td>
</tr>
<tr>
<td>Subtype 3: Phymatous Rosacea</td>
<td>Thickened, coarse skin; enlarged pores; tissue hyperplasia; nodules.</td>
</tr>
<tr>
<td>Subtype 4: Ocular Rosacea</td>
<td>Burning, stinging, dryness; foreign-body sensation; ocular photosensitivity; Telangiectases of the conjunctiva may be present.</td>
</tr>
<tr>
<td>Variant – Granulomatous</td>
<td>Hard yellow, brown, or red cutaneous papules or nodules. Lesions may be less inflammatory than papules or pustules, and size may vary among patients. Presence of other rosacea signs not necessary for this diagnosis.</td>
</tr>
</tbody>
</table>

In order to make a diagnosis of rosacea, at least one of the following primary features is required (with a central face distribution):³

- Transient erythema, or flushing
- Nontransient erythema, or persistent redness of the facial skin
- Red papules, appearing with or without pustules
- Telangiectasia

The following are secondary signs and symptoms that may accompany primary features of rosacea:³

- Burning/stinging
- Elevated red plaques
- Dry, rough, or scaling appearance (central face)
- Edema
- Ocular manifestations (eg, burning, conjunctival hyperemia, styes, lid inflammation)
- Peripheral location
- Phymatous changes

Pathogenesis of Rosacea

The pathogenesis of rosacea is poorly understood and continues to be an area of great controversy. A variety of hypotheses have been proposed for the underlying cause of the constellation of clinical features of rosacea, though it is presumed, at least partially, to be a vascular response that is somehow genetically determined. Four major components of rosacea — vascular, ³Wilkin J, Dalil M, Detmer M, et al. Standard classification of rosacea: report of the National Rosacea Society Expert Committee on the Classification and Staging of Rosacea. J Am Acad Dermatol. 2002;46:844-847.
inflammatory, sebaceous, ocular — are independently apparent and clinically correlated with various manifestations of rosacea (Figure 1). However, it is not entirely clear how these components may be interrelated. The vascular component correlates with erythema, flushing, telangiectasia, and edema. The inflammatory component corresponds to perilesional erythema, papules, pustules, and edema. The sebaceous component reflects phymas, whereas the ocular component is associated with blepharitis, conjunctivitis, and keratitis.

Numerous etiologic factors have been proposed for rosacea, including genetic predisposition, vascular dysfunction, Demodex folliculorum mites, Helicobacter pylori, light exposure and photodamage, and psychogenic factors.

- **Genetic Predisposition**
  
  A primary genetic cause has been suggested because single genes often control such mediators as enzymes, neuroendocrine transmitters, and cytokines, which are all present in rosacea pathways. There is a known genetic predisposition to flushing, which is an early manifestation of rosacea. The underlying genetic component may be combined with certain environmental factors that further produce inflammation, as well as vascular lability and proliferation.
• Vascular Dysfunction

It has been proposed that facial rosacea is a cutaneous vascular dysfunction, leading to the characteristic blushing or flushing as a result of dilated blood vessels, although this has not been verified. The common occurrence of migraines in persons with rosacea further suggests that a vascular abnormality may be an important underlying factor in this syndrome.

• Inflammation

Inflammatory cells such as neutrophils and the release of inflammatory mediators such as substance P, histamine, bradykinin, and prostaglandins are considered key pathophysiologic factors in the development of rosacea.

• Demodex mites

D. folliculorum, a commensal skin mite that lives in facial hair follicles, has been linked to rosacea. The presence of D. folliculorum may be an important component related to the inflammatory reaction; however, there is no consensus as to what degree these mites are causative of the skin pathology in rosacea.

• H. pylori

H. pylori is a gram-negative bacterium that colonizes the gastric mucosa. Strongly associated with peptic ulcer disease, H. pylori has also been implicated in a number of extra-gastrointestinal disorders, including rosacea. Although the exact role of H. pylori in extra-gastrointestinal disorders is not clear, it has been hypothesized that this organism induces a systemic inflammatory response via substances such as cytokines and vasoactive toxins. It has also been suggested that H. pylori synthesizes gastrin, a hormone that stimulates flushing.

• Light Exposure and Photodamage

Rosacea is among many dermatologic conditions that are photoaggravated. Ultraviolet light affects blood vessel function by altering elastic and collagen fibers, thus weakening the integrity of vasculature and leading to the increased responsiveness of facial microvasculature that is prominent in rosacea. Reactive oxygen species (ROS) released after exposure to ultraviolet radiation may be involved in rosacea pathophysiology.

• Psychogenic Factors

Emotional stress is thought to play a major role in triggering the flare-ups of rosacea. In a survey of more than 700 rosacea patients, 91% reported that emotional stress at least sometimes caused their rosacea to flare up, and 83% reported that incorporating stress management techniques decreased or sometimes reduced their rosacea flare-ups.
Treatment of Rosacea

Treatment Goals
Many individuals with rosacea are underrecognized and undertreated, and thus do not have information or expectations of their dermatologic condition. Patients must be educated that their condition is not curable, but is treatable, and that long-term therapy is usually required.

The following are considered important treatment goals for rosacea:

- Avoid or modify exacerbating factors
- Decrease facial erythema
- Reduce the number of papules and pustules
- Maintain remission

Selection of Therapy
The availability of multiple agents for the treatment of rosacea often complicates selection of an appropriate agent. Currently, there is no universally accepted algorithm for the treatment of rosacea. Initial selection of a therapeutic agent is therefore based upon disease severity. Figure 2 provides a treatment algorithm for managing rosacea. For cases of mild-to-moderate rosacea, as illustrated in Figures 3 and 4, topical therapy alone may be used effectively. Oral antibiotic therapy may be combined with topical treatment initially to hasten response, followed by tapering of the oral agent.

Figure 2. Rosacea Therapy Medical Treatment Tier

- Oral Antibiotic May Be Tapered Slowly Based on Response
- Attempt to Maintain Long-Term Control With Topical Therapy

For cases of moderate-to-severe rosacea as shown in Figures 5 and 6, oral antibiotic therapy may be utilized in combination with topical therapy. Fixed telangiectases do not respond to medical therapy and often require directed laser or light (i.e., intense pulsed light) therapy. Rhinophyma usually requires laser therapy or surgical intervention.
Topical Therapy

Primary or first-line treatment of rosacea generally involves topical therapy, with the possible addition of an oral antibiotic. The efficacy of topical therapy for rosacea correlates with a reduction in erythema, number of inflammatory lesions (papules, pustules), and intensity and/or frequency of flares. The topical agents approved for rosacea, listed and reviewed in order of their US market availability, include 10% sodium sulfacetamide with 5% sulfur, 0.75% and 1% metronidazole, and 15% azelaic acid (Table 2). Most newer topical agents are the result of advances in formulation science, which produced vehicles with enhanced cosmetic elegance and greater skin tolerability.

<table>
<thead>
<tr>
<th>Topical Agent</th>
<th>Preparation/Manufacturer</th>
<th>Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfacetamide 10%/sulfur 5%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creams</td>
<td>Clenia® (Upsher-Smith Laboratories, Inc.)</td>
<td>Efficacy in reducing lesions, erythema and symptoms</td>
</tr>
<tr>
<td></td>
<td>Rosacea® Cream with Sunscreens (Stribel Laboratories, Inc.)</td>
<td>SPF 18 UVA-UVB sunscreen in Rosacea® Cream with sunscreens</td>
</tr>
<tr>
<td>Mask</td>
<td>Plexon SCT® (Medicis Pharmaceutical Corporation)</td>
<td>Mask for short-contact therapy (Plexon SCT®)</td>
</tr>
<tr>
<td>Gels</td>
<td>Avar® Gel/Avar® Green (Sirius Laboratories)</td>
<td>Well tolerated</td>
</tr>
<tr>
<td></td>
<td>Rosul® Gel (Bradley Pharmaceuticals, Inc.)</td>
<td>Contraindicated in patients with hypersensitivity to sulfonamides</td>
</tr>
<tr>
<td>Lotions</td>
<td>Rosul® (Dock Dermatologics)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>SulfaCet-R® (Dermik Laboratories)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Flexion® Topical Suspension (Medicis Pharmaceutical Corporation)</td>
<td></td>
</tr>
<tr>
<td>Topical Cleansers</td>
<td>Clenia® Cleanser (Upsher-Smith Laboratories, Inc.)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Flexion® Cleanser (Medicis Pharmaceutical Corporation)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Rosanil® Cleanser (Galderma Laboratories, L.P)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Rosul® Cleanser (Bradley Pharmaceuticals, Inc.)</td>
<td></td>
</tr>
<tr>
<td>Metronidazole 0.75%</td>
<td>MetroCream® (Galderma Laboratories, L.P)</td>
<td>Anti-inflammatory action</td>
</tr>
<tr>
<td></td>
<td>MetroGel® (Galderma Laboratories, L.P)</td>
<td>Efficacy in reducing lesions, erythema and symptoms well documented</td>
</tr>
<tr>
<td></td>
<td>MetroLotion® (Galderma Laboratories, L.P)</td>
<td>Well tolerated</td>
</tr>
<tr>
<td>Metronidazole 1%</td>
<td>Noritate® Cream (Dermik Laboratories)</td>
<td></td>
</tr>
<tr>
<td>Azelaic acid gel 15%</td>
<td>Finacea® Gel (Berlex, Inc.)</td>
<td>Anti-inflammatory action</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Efficacy in reducing lesions, erythema and symptoms well documented</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Well tolerated</td>
</tr>
</tbody>
</table>
Sodium Sulfacetamide 10%/Sulfur 5%

The combination of sodium sulfacetamide and sulfur has been used in dermatology for five decades, first for the treatment of acne vulgaris, then for seborrheic dermatitis, and later for rosacea. This combination product and its formulations are unique in its dual utility as a "leave on" topical therapy and therapeutic cleanser. Although data are limited on mechanism of action for inflammatory facial dermatoses, sodium sulfacetamide competitively antagonizes PABA, an essential component for bacterial growth, whereas sulfur has been reported to inhibit Propionibacterium acnes (P. acnes) growth and the formation of free fatty acids. Sulfacetamide 10%/sulfur 5% is available in an extensive array of vehicles including creams, gels, lotions, and cleansers, allowing many cosmetic choices for individualizing treatment of rosacea. Both the "leave on" (lotions, creams, gels) and cleanser formulations of sulfacetamide/sulfur appear to be beneficial in patients who present with overlapping seborrheic dermatitis and rosacea.

A number of new sulfacetamide/sulfur preparations have become available only within the past few years, including several gels and cleansers, an emollient cream, and a sunscreen-containing cream. A tinted sulfacetamide/sulfur gel (Avar™ Green) utilizes the concept of green over red to camouflage the erythema and thus create the perception of a neutral tone. A silica-based mask formulation (Flexion SCT™) is available for short-contact therapy, especially in patients with oily skin or "stubborn" inflammatory lesions. Another new sulfacetamide 10%/sulfur 5% cream (Rosac® Cream with sunscreens) contains two non-PABA sunscreen agents, avobenzone and octinoxate, and has demonstrated marked efficacy in one trial, with results superior to those achieved with metronidazole 0.75% cream.

Metronidazole

Since its approval in 1989, topical metronidazole has been widely used as a first-line topical agent for the treatment of rosacea. Numerous studies have evaluated and confirmed the efficacy of metronidazole 0.75% and 1% formulations (MetroGel®, MetroCream™, MetroLotion®, Noritate®) for the treatment of rosacea. The efficacy of metronidazole application does not appear to relate to antimicrobial activity, rather, to its anti-inflammatory and antioxidant properties. In vitro data suggest that topical metronidazole possesses antioxidant activity, which may subdue oxidative tissue damage and also prevent and treat rosacea symptoms. Topical metronidazole has consistently demonstrated statistically significant superiority compared with vehicle. Most studies also noted statistically significant symptom reduction, with improvements reported in 54%-88% of patients treated with
metronidazole. The cream, gel, and lotion formulations of metronidazole have all demonstrated comparable efficacy and good tolerability. The most prominent side effects are localized reactions, and systemic side effects are notably absent with topical metronidazole. The value of topical metronidazole for maintenance therapy of rosacea has been confirmed.

**Azelaic Acid Gel**

Azelaic acid, a naturally occurring dicarboxylic acid, formulated as a 15% aqueous gel (Finacea®) is the newest therapeutic agent to be approved for the treatment of rosacea in more than a decade. Azelaic acid has been reported to have anti-inflammatory, antibacterial, comedolytic, and bleaching properties. The anti-inflammatory mechanism of azelaic acid, similar to metronidazole, is attributed in part to inhibition of neutrophil-mediated ROS. The clinical efficacy of azelaic acid 15% gel was demonstrated in two pivotal, 12-week, double-blind, vehicle-controlled studies (n=664), and in a 15-week comparative study with metronidazole 0.75% gel (n=251). In the 12-week studies, twice-daily treatment with azelaic acid gel yielded statistically significantly higher reductions in mean inflammatory lesion count than vehicle (P=0.001), and significantly higher numbers of patients treated with azelaic acid gel experienced improvement in erythema compared with vehicle (P=0.001). In the 15-week study, azelaic acid 15% gel demonstrated a distinct therapeutic advantage over metronidazole gel in reduction of mean normal lesion count, mean percent decrease in inflammatory lesions, and erythema severity. Whereas the effectiveness of metronidazole gel appeared to plateau after week 8 in this trial, azelaic acid gel maintained improvement through week 15.

Mild, transient sensory symptoms may be observed in some patients upon application of azelaic acid, likely related to the particulate nature of this drug. In the pivotal trials described here, reported adverse events such as burning, stinging, tingling, or itching were mild and transient in the majority of patients. Local tolerability of azelaic acid gel was rated as ‘good’ or ‘acceptable despite minor irritation’ by 40%-50% of patients in the two 12-week studies, whereas approximately 90% of patients in the 15-week study rated azelaic acid as ‘good’ or ‘acceptable despite minor irritation’. In clinical practice, the tolerability of azelaic acid 15% gel is overall very favorable.
Topical Investigational Agents

Tacrolimus and Pimecrolimus
Steroid-induced rosaceaiform eruption (not a variant of rosacea) can occur as a paradoxical, inflammatory response in any patient during or after chronic topical corticosteroid use. Tacrolimus 0.1% and 0.03% ointment (Protopic) and pimecrolimus 1% cream (Elidel) are two relatively new macrolide nonsteroidal immunomodulators approved for moderate-to-severe atopic dermatitis, which may show promise for steroid-induced rosacea. These agents act by inhibiting the phosphatase calcineurin, and modulate inflammatory responses by inhibiting T-cell activation and cytokine production.23,24 In a preliminary study of three patients with steroid-induced rosacea who applied a 0.075% tacrolimus preparation twice daily, pruritus, tenderness, and erythema were resolved after 7-10 days of consecutive use of this agent.26 Although clinical trials of tacrolimus ointment for non-steroid-induced rosacea have not been performed, some investigators suggest that standard topical therapies appear to control rosacea symptoms faster and more effectively than tacrolimus ointment, while another report described exacerbation of rosacea by topical tacrolimus.26,27

Tretinoin
Topical retinoids such as retinoic acid and vitamin A derivatives are approved for the treatment of acne, and are sometimes used as adjunctive therapy in cases of severe or recalcitrant rosacea when antibiotic therapy has failed.28 Retinoids are the only topical treatment currently available that promote dermal connective tissue remodeling, thus helping to reverse photodamage-related effects seen in rosacea patients.29 Topical retinaldehyde, a retinoic acid precursor with therapeutic activity similar to retinoic acid, demonstrated beneficial effects on the vascular component of rosacea and good tolerability in a 6-month study of 23 women.30 At 5 months, 75% of the patients with erythema achieved a clinical response with once-daily application of retinaldehyde.

The use of topical retinoids in the management of rosacea remains somewhat controversial and relatively unsupported in the medical literature, secondary to claims that these agents actually exacerbate the underlying inflammatory reaction of rosacea and may cause angiogenesis.31 In light of such concerns, most patients can tolerate a topical retinoid if treatment is started with a low-potency preparation and gradually increased in frequency over 3-4 weeks, allowing the skin to acclimate to the effects of the retinoid. Most patients require initiation of a topical retinoid every other or every third night.
Oral Therapy

Oral antibiotics have been a mainstay of treatment of rosacea for many years, and appear to be most effective in managing the papulopustular form. Oral antibiotics are frequently prescribed at relatively high doses until rosacea symptoms are controlled, and then reduced to a maintenance dose. A duration of 3-6 months of oral antibiotic therapy is generally required. Approximately 25% of patients relapse within 1 month after discontinuation of active therapy with tetracyclines, approximately 50%-60% at 6 months, and approximately 70% by 1-4 years in the absence of maintenance therapy.31

Table 3 details various oral therapies to consider for the treatment of rosacea.

<table>
<thead>
<tr>
<th>Category</th>
<th>Preparations/Strength</th>
<th>Starting/Maintenance Dosages</th>
<th>Comments/Precautions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tetracyclines</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tetracycline</td>
<td>Achromycin V Capsules (250, 500 mg)</td>
<td>250 mg QID</td>
<td>- Doxycycline associated with photosensitivity</td>
</tr>
<tr>
<td>Minocycline</td>
<td>Dynacin® Tablets (50, 75, 100 mg)</td>
<td>500-500 mg QD</td>
<td>- Contraindicated in pregnancy women</td>
</tr>
<tr>
<td>Doxycycline</td>
<td>Minocin® Capsules</td>
<td></td>
<td>- Minocycline associated with vertigo, hypopigmentation,</td>
</tr>
<tr>
<td>monohydrate</td>
<td>Adoxor® Tablets (50 mg, 75 mg, 100 mg)</td>
<td></td>
<td>rare hypersensitivity syndrome and drug-induced lupus</td>
</tr>
<tr>
<td></td>
<td>Doryx® Capsules</td>
<td></td>
<td>(chronic therapy)</td>
</tr>
<tr>
<td><strong>Subantimicrobial dose</strong></td>
<td>Penostat (20 mg)</td>
<td>20 mg BID</td>
<td>- Little to no risk of photosensitivity</td>
</tr>
<tr>
<td><strong>Doxycycline hylate</strong></td>
<td></td>
<td>20 mg BID</td>
<td>- Not associated with development of antimicrobial</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>resistance</td>
</tr>
<tr>
<td><strong>Macrolides</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Erythromycin</td>
<td>Eryc®, E.E.S.®, E-Mycin®, Erythrocin®, Isox® (250 mg, 333 mg, 400 mg, 500 mg)</td>
<td>250-500 mg BID-TID</td>
<td>- Most common side effects are gastrointestinal</td>
</tr>
<tr>
<td></td>
<td></td>
<td>250-500 mg QID-QID-QID</td>
<td>- Potential drug interactions</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>Flagyl® (250 mg)</td>
<td>250-500 mg QD for 2-8 weeks</td>
<td>- Associated with intense toxicity when combined with</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>alcohol intake; best utilised as alternative oral</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>therapy in refractory cases</td>
</tr>
<tr>
<td>Isotretinoin</td>
<td>Accutane® (10 mg, 20 mg, 40 mg)</td>
<td>0.2-1.0 mg/kg daily variable duration based on clinical judgment (usual duration of 20 weeks or to maximum total dose of 150 mg/kg)</td>
<td>- Should be reserved for severe cases and those resistant to oral antibiotics</td>
</tr>
<tr>
<td></td>
<td>Accutane® (10 mg, 20 mg, 40 mg)</td>
<td>0.2-1.0 mg/kg daily variable duration based on clinical judgment (usual duration of 20 weeks or to maximum total dose of 150 mg/kg)</td>
<td>- Patients should avoid intake of vitamins or food</td>
</tr>
<tr>
<td></td>
<td>Amnesteem®</td>
<td></td>
<td>supplements containing vitamin A</td>
</tr>
<tr>
<td></td>
<td>Soriat®</td>
<td></td>
<td>- Highly teratogenic, should be used with</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>great caution in women of childbearing age</td>
</tr>
</tbody>
</table>

31. Biswas B. Subantimicrobial dose doxycycline for acne
Oral Tetracyclines
The efficacy of tetracyclines in the treatment of rosacea has been well documented in numerous randomized controlled trials. Tetracycline has been considered the standard of oral antibiotic therapy for rosacea for many years; the second-generation tetracyclines minocycline and doxycycline are effective in the treatment of rosacea. Tetracyclines and other oral antibiotics treat papulopustular rosacea effectively, but have little effect on telangiectasia. Tetracyclines appear to work in rosacea primarily by reducing inflammation, and possibly by counteracting neutrophil chemotaxis, macrophage activation, cytokine signaling, or activation of complement or protein kinase C.

Subantimicrobial Dose Doxycycline (SDD)
Tetracyclines inhibit connective tissue breakdown by several mechanisms, including direct inhibition of matrix-degrading metalloproteinases (MMPs). Treatment of chronic disorders such as periodontitis was limited by the potential for development of microbial resistance; however, preclinical and early clinical studies suggested that a subantimicrobial dose (20 mg twice daily) of doxycycline (SDD), the most potent inhibitor of MMP activity, was effective without producing a detectable effect on the microflora. This concept has been used successfully in the treatment of rosacea. In an open-label study of 50 rosacea patients treated with SDD, an 80%-100% clearing of inflammatory lesions and a 50% reduction in erythema was observed.

Oral Macrolides
The macrolide erythromycin has been used as an alternative when patients are intolerant or allergic to the tetracyclines. The second-generation macrolides clarithromycin and azithromycin have also demonstrated efficacy in the treatment of rosacea, showing reduction in erythema and papules and favorable tolerability. Both erythromycin and clarithromycin may be associated with significant drug-drug interactions, including contraindicated use with atorvastatin, simvastatin, and lovastatin (cholesterol-lowering agents).

Oral Metronidazole
Oral metronidazole has been considered an effective alternative in the treatment of rosacea, and has been particularly useful in reducing rosacea signs and symptoms when used to treat concomitant H. pylori infection in such patients. However, long-term therapy with metronidazole is considered a poor choice, given its toxicity if taken with alcohol. It may be best utilized as second-line oral therapy when other antibiotics have failed.

**Oral Isotretinoin**

Oral isotretinoin (Accutane®) has been used effectively in some cases of rosacea, especially those unresponsive to oral antibiotic therapy. Treatment with low-dose isotretinoin sometimes requires several months of therapy for true benefits to be realized, and careful consideration should be given with regard to its clinical benefit versus risk. Isotretinoin has several mechanisms of action, among them modification of cutaneous facial blood flow, which may be critical to its success in the treatment of rosacea.13 Because this agent is highly teratogenic, it must be used with utmost caution in women of childbearing potential, and should be avoided in those of childbearing age whose use of contraceptives is uncertain.

**Physical Modalities**

*Laser therapy*

Laser therapy, which uses multiple wavelengths of light to treat dilated facial blood vessels, was implemented in the 1980s, and has since evolved to include many different phototherapy devices and therapeutic targets. Known for its effectiveness in treating telangiectases that are not responsive to topical or oral therapy, laser therapy now has a broader scope, including remodeling of dermal connective tissue and strengthening of the epidermal barrier.19 Vascular types of lasers used to treat erythema and telangiectasia include pulsed-dye laser (PDL), long-pulsed-dye lasers, the potassium-titanyl-phosphate (KTP) laser, and the diode-pumped frequency-doubled laser.20-30 Treatments with laser therapy generally take 15-30 minutes, and may be performed every 6-12 weeks. Although laser therapy has produced significant reductions in rosacea, small spot size and the propensity for purpura development may limit patient acceptance of these systems.29

Intense pulsed light (IPL) therapy represents a revolutionary approach to rosacea treatment. This type of nonablative facial rejuvenation is based on emitting high-intensity polychromatic pulses of light (not lasers) to penetrate the skin and eliminate visible signs of rosacea. IPL induces cytokine activation and growth factor release, which in turn contribute to collagen and vascular remodeling. IPL is a good option for patients with treatment-resistant rosacea, treatment-plateaued rosacea, or an aversion to chronic oral therapy.9 Other potential advantages of IPL over vascular laser therapy include a larger spot size to treat bigger areas, the ability to treat larger and deeper vessels, and promotion of dermal collagen remodeling.13
Following IPL therapy in 32 rosacea patients, 83% had reduced erythema, 75% had reduced flushing and improved skin texture, and 64% had fewer acneiform breakouts. In a much larger study, 93% of 188 patients achieved 75%-100% clearance in one to four treatment sessions with IPL (PhotoDerm™ VL [vascular lesions]), without any scarring or permanent side effects.

**Other Therapies**

Limited data are available on the use of topical antibiotics for the treatment of rosacea. Topical clindamycin or erythromycin are generally used as secondary options or adjunctive therapy in the treatment of rosacea. Twicely-daily application of either agent has been shown to be effective. In most patients with rosacea, use of an aqueous-based gel or lotion is preferred over an alcohol-based solution or gel in order to reduce the potential for irritation and erythema. Sporadic reports of rosacea treatment have been published with benzoyl peroxide, sulfur, tretinoin, permethrin, bifonazole and ketoconazole. The clinical benefit of sulfur and permethrin may in some cases relate to reduction in Demodex mites.

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