CLINICAL PRACTICE

Caren G. Solomon, M.D., M.P.H., *Editor*

Rosacea

Esther J. van Zuuren, M.D.

This Journal *feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the author's clinical recommendations.*

From the Department of Dermatology, Leiden University Medical Center, Leiden, the Netherlands. Address reprint requests to Dr. van Zuuren at the Dermatology Department B1-Q, Leiden University Medical Center, Albinusdreef 2, 2333 ZA Leiden, the Netherlands, or at e.j.van_zuuren@lumc.nl.

N Engl J Med 2017;377:1754-64.
DOI: 10.1056/NEJMcp1506630

A 36-year-old woman presents with facial redness, numerous papules and pustules on the face, and a history of repeated episodes of minimal flushing, all of which become more marked during the summer months. She is troubled by her appearance and is starting to avoid social events. Treatment with 0.75% metronidazole gel applied twice daily reduced the number of lesions in the past, but the lesions recurred within several weeks after she stopped treatment. How should the patient's case be managed?

THE CLINICAL PROBLEM

An audio version of this article is available at NEJM.org

Rosacea is a chronic, inflammatory skin disease that affects primarily the cheeks, nose, chin, and forehead.[1] Manifestations include persistent facial erythema, papules, pustules, telangiectasia, and recurrent flushing. Phymatous changes (hypertrophy of the sebaceous glands and fibrosis) can also occur, the most common of which is rhinophyma (bulbous nose).[1] Involvement of the eyes (ocular rosacea) is estimated to occur in up to three quarters of patients with rosacea and frequently includes foreign-body sensation, dryness, burning, itching, redness, photophobia, tearing, and blurred vision.[2] Sight-threatening keratitis is rare. The red, pimply facial rash can cause embarrassment, low self-esteem, and anxiety and may lead to feelings of depression and stigmatization, with a marked negative effect on quality of life.[3-5] The condition usually starts in affected persons when they are between 30 and 50 years of age and is characterized by episodes of exacerbation and remission.[6] Women are more commonly affected than men, and rosacea has been shown to be particularly common among fair-skinned people of Celtic origin.[6] The prevalence of rosacea across populations has been reported to range from less than 1% to 22%.[7]

Rosacea has been classified by the National Rosacea Society Expert Committee (www.rosacea.org/) into four subtypes: erythematotelangiectatic (Fig. 1A), papulopustular (Fig. 1B), phymatous (Fig. 2A), and ocular (Fig. 2B and 2C).[8] According to this classification, the presence of at least one of the following primary features in a central distribution on the face is diagnostic of rosacea: flushing (transient erythema), nontransient erythema, papules and pustules, and telangiectasia. Secondary features, which can appear concurrently or independently, include a burning or stinging sensation, plaque, a dry appearance of the skin, edema, ocular manifestations, occurrence in a location other than the face, and phymatous changes.[8] Given that rosacea often spans more than one subtype, that it can progress be-

KEY CLINICAL POINTS

ROSACEA

- Rosacea is a common, chronic facial skin disease that can have an adverse effect on quality of life; it affects more women than men.
- The diagnosis is made clinically, and management consists of education, the avoidance of triggers that can exacerbate the condition, skin care measures, and various treatment options.
- Erythema can be treated with topical brimonidine, topical oxymetazoline, laser therapy, or other light-based therapies.
- For inflammatory lesions, first-line therapies include topical ivermectin, topical azelaic acid, or topical metronidazole. Treatment with modified-release oral doxycycline at a dose of 40 mg, oral tetracycline, or low-dose oral isotretinoin is recommended for moderate-to-severe inflammatory lesions and for inflamed phymas; fibrotic phymas can be treated with surgical therapies or ablative laser therapy.
- For ocular rosacea, eyelid hygiene and the use of artificial tears are recommended. More severe forms of ocular rosacea can be treated with cyclosporine eyedrops, fusidic acid gel or metronidazole gel applied to the eyelids, or oral doxycycline. Referral to an ophthalmologist may be warranted.
- Maintenance therapy is recommended, preferably with the use of a topical treatment.

tween subtypes, and that certain findings are pathognomonic (such as phymatous changes), the international Rosacea Consensus (ROSCO) panel recently proposed a different classification strategy — one that is based on phenotype and that more adequately covers the diversity of clinical presentations. However, this strategy has not yet been widely adopted.[9] (The ROSCO panel, which comprised 17 dermatologists and 3 ophthalmologists, aimed to establish international consensus on rosacea with respect to diagnosis and determination of severity to improve outcomes in patients with rosacea. The planning and delivery of the project was funded by Galderma, but Galderma was not involved in the voting, discussion, or handling of data.)

The pathophysiology of rosacea remains uncertain. Genetic factors, dysregulation of the innate and adaptive immune system, vascular and neuronal dysfunction, and microorganisms such as *Demodex folliculorum* appear to be involved. Triggers such as heat, stress, ultraviolet light, spicy food, hot beverages, smoking, and alcohol may exacerbate symptoms.[1,10-12] Rosacea is associated with impairment of the skin barrier, which results in excess transepidermal water loss, making the skin dry, prone to scaling and peeling, and sensitive to burning and stinging.[13,14]

STRATEGIES AND EVIDENCE

DIAGNOSIS

The diagnosis of rosacea is based on clinical features and careful history taking. A skin-biopsy specimen is obtained only to rule out other diagnoses, since the histopathological features of rosacea are typically not specific to rosacea.[11] The differential diagnosis includes seborrheic dermatitis, flushing disorders, acne vulgaris, perioral dermatitis, lupus erythematosus, and chronic actinic damage.[6,13] Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org, provides an overview of the distinguishing features of rosacea.

MANAGEMENT

General Measures and Skin Care

Management of rosacea usually starts with educating patients about the skin condition and potential exacerbating factors to help patients identify triggers and improve their coping mechanisms.[6,11,15,16] Although randomized trial data are lacking, clinical experience supports several general measures for skin care.[6,11,13,15,16] Maintaining a diary is a useful means of identifying stimuli and triggers that can exacerbate rosacea (Table 1). Given the impairment of the skin-barrier function, irritant cosmetic products should be avoided. Ultraviolet light is a well-known trigger for rosacea; therefore, the daily use of sunscreens is recommended.[6,14,16]

Treatments for Flushing, Erythema, and Telangiectasia

Randomized trial data on interventions for transient erythema and flushing are lacking.[1] However, on the basis of empirical evidence, when flushing is bothersome, beta-blockers (e.g., nad-

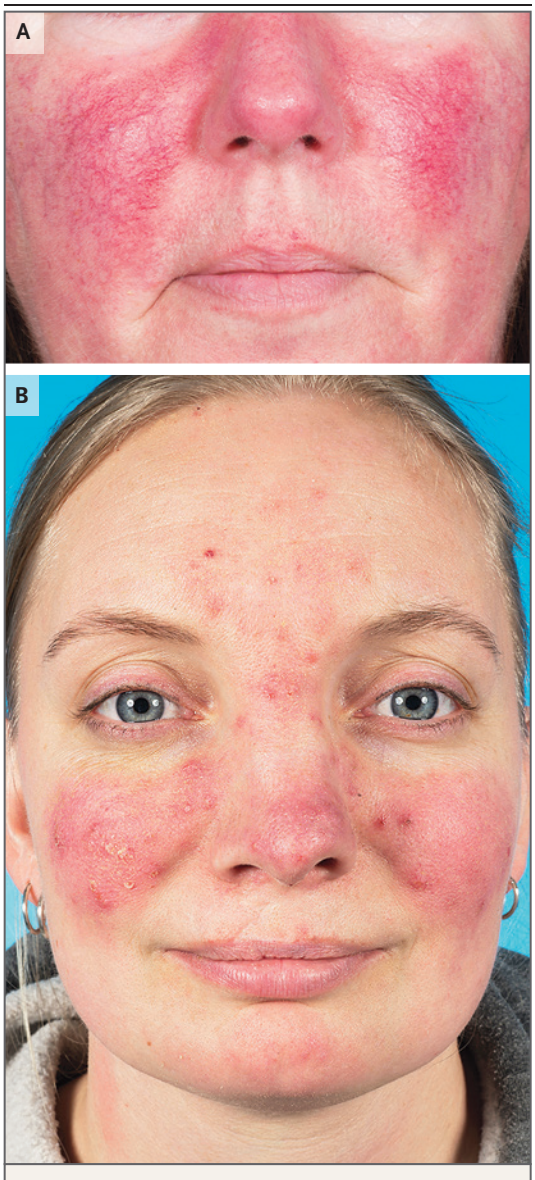

Figure 1. Erythematotelangiectatic and Papulopustular Rosacea.

Panel A shows a patient with erythematotelangiectatic rosacea, in which diffuse erythema and telangiectasia are present on the cheeks and nose (i.e., convex areas of the face). Panel B shows a patient with papulopustular rosacea, in which erythema and papules are evident, as well as dry scaling on the forehead, nose, and cheeks (i.e., central convex areas of the face); the periocular area is spared.

olol, propanolol, and carvedilol) or α_2-adrenergic agonists (e.g., clonidine) are often prescribed (Table 2).[6,10,14,15] Treatment with 0.5% brimonidine tartrate gel, a highly selective α_2-adrenergic agonist with vasoconstrictive activity, was shown to reduce persistent erythema in two randomized, controlled trials involving a total of 553 patients.[20] In a Cochrane meta-analysis that included the two trials, a reduction in erythema was reported in 41% of the patients in the brimonidine group as compared with 20% of the patients who received vehicle (risk ratio, 2.11; 95% confidence interval [CI], 1.60 to 2.78).[1] After brimonidine was applied to the face, improvement was visible within 30 minutes and peaked between 3 and 6 hours after application, after which the effects progressively diminished. Immediate side effects included erythema, pruritus, a burning sensation, and flushing; rebound erythema associated with the use of brimonidine can also occur. Treatment with 1% oxymetazoline hydrochloride cream, an α_1-adrenergic agonist and a partial α_2-adrenergic agonist, has recently been approved by the Food and Drug Administration (FDA) for the treatment of persistent erythema associated with rosacea on the basis of two randomized, controlled trials involving a total of 885 participants.[21] In both trials, the percentage of patients who had a reduction in erythema was significantly higher among patients who received oxymetazoline than among those who received vehicle (12% vs. 6%, P=0.03, at 3 hours postdose in one trial and 14% vs. 7%, P=0.02, at 3 hours postdose in the other trial).

Although laser therapy and other light-based therapy are widely used in the treatment of erythema and telangiectasia, these methods of treatment have been investigated primarily in observational studies. The few randomized trials from which data are available are hampered by small sample sizes.[1,6,15,41]

Treatments for Inflammatory Lesions

Treatments for inflammatory papules and pustular lesions depend on the severity of the inflammation. Topical azelaic acid, topical metronidazole, and topical ivermectin are all first-line treatment options.[1,15] In two randomized, controlled trials involving a total of 1371 patients, treatment with topical ivermectin was associated with greater reductions in the number of inflammatory lesions over the course of 12 weeks than those observed with vehicle (66% vs. 39% in one trial and 70% vs. 42% in the other trial).[1,22] The use of topical azelaic acid (15% gel, 15% foam, or 20% cream twice daily for 12 weeks) was evaluated in five randomized, controlled trials,[23,42-44] involving a total of 1245 patients, and consistently resulted in a reduction in disease severity,

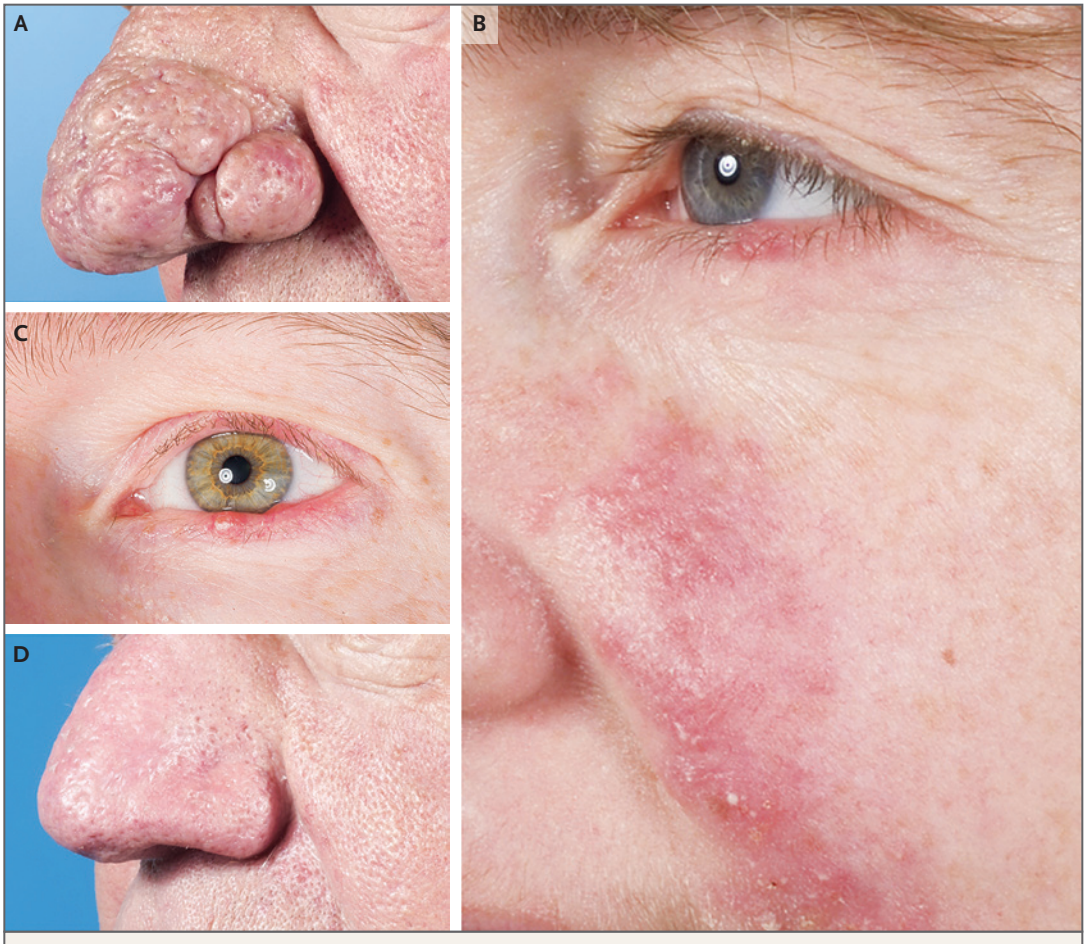

Figure 2. Phymatous and Ocular Rosacea.

Panel A shows a patient with rhinophyma, in which hypertrophy of the sebaceous glands of the nose and fibrosis result in enlargement and distortion of the nose. Panel B shows a patient who has rosacea with ocular involvement; mild erythema accompanied by a few papules can be seen on the cheeks, and pustules and inflammation are present on the lower eyelid. Panel C shows a patient with ocular rosacea, in which minimal blepharitis and a chalazion at the lower eyelid can be seen; the patient also has mild rosacea of the skin with erythema, telangiectasia, and a few papules and pustules. Panel D shows the patient in Panel A after one electrosurgical procedure; prominent pores are still visible.

Table 1. General Measures and Skin Care Guidelines for the Management of Rosacea.*

Advise patients to keep a diary to identify stimuli and triggers that can exacerbate rosacea (e.g., cosmetics, weather conditions, exercise, drugs, spicy food, beverages, alcohol, and stress). Advise patients to avoid the identified triggers.
Suggest the daily use of sunscreens that protect against exposure to ultraviolet A and ultraviolet B radiation, have a sun protection factor of 30 or greater, and preferably contain dimethicone, cyclomethicone, or both to mitigate facial irritation. Sunscreens containing zinc oxide or titanium are generally associated with few unacceptable side effects.
Suggest the use of soap-free cleansers and non-oily moisturizers. Many moisturizers have been developed for the sensitive and easily irritated skin of patients with rosacea; sometimes these products contain green pigment to neutralize facial redness.
Suggest the use of oil-free foundation and concealer when the use of these products is desired.
Advise patients to generally avoid the following skin care products:
Waterproof make-up, which can be difficult to remove.
Skin tonics, toners, and astringents (i.e., products that contain alcohol, menthol, peppermint, camphor, witch hazel, or eucalyptus oil).
Cosmetics containing sodium lauryl sulphate, strong fragrances, fruit acids, or glycolic acids.
Exfoliating scrub cream.

* This table is adapted from Elewski et al.,[6] Two et al.,[14] and Powell.[16]

Table 2. Recommended First-Line Treatment Options for Rosacea, According to Phenotypic Features.*

Phenotypic Feature and Treatment	Dosage	Common Side Effects	Evidence†
Flushing			
Beta-blockers			Case series[6,14,15]
Propanolol	20 to 40 mg 2 to 3 times per day	Hypotension, bradycardia, dizziness	
Carvedilol	6.25 mg 2 to 3 times per day	Hypotension, bradycardia, dizziness	
α_2-Adrenergic agonists			
Clonidine	50 μg twice daily	Hypotension, bradycardia, dizziness, sedation, lethargy, headache, upper abdominal pain	Case series[6,14,15]
Erythema			
Brimonidine (0.33% gel)‡§ Mirvaso top qd 30gm $485	Pea-sized amount applied to the face, with avoidance of the eyes and lips, once daily; evaluate after 6 to 8 wk	Erythema, flushing, skin burning, contact dermatitis, rebound erythema	High-quality evidence[1,20]
Oxymetazoline hydrochloride (1% cream)‡¶ Rhofade qd 30gm $495	Pea-sized amount applied to the face, with avoidance of the eyes and lips, once daily; evaluate after 6 to 8 wk	Contact dermatitis, worsening inflammatory lesions, pruritus, pain, erythema	Randomized, controlled trials[21]
Intense pulsed light therapy, pulsed dye laser treatment	Usually 1 to 4 treatments, with 3 to 4 wk between treatments	Pain (cooling of the skin during or after treatment helps alleviate the pain), transient erythema, edema and purpura, hypopigmentation or hyperpigmentation; scarring is rare	Low-quality evidence[1]
Telangiectasia			
Electrodessication	Depends on severity	Pain, crusts	Expert opinion[15]
Intense pulsed light therapy, pulsed dye laser treatment, Nd:YAG laser therapy, or other laser therapy	Usually one to four treatments, with 3 to 4 wk between treatments	Pain (cooling of the skin during or after treatment helps alleviate the pain), transient erythema, edema and purpura, hypopigmentation or hyperpigmentation; scarring is rare	Low-quality evidence[1]
Inflammatory lesions (papules and pustules)			
Topical treatment (usually sufficient for mild disease)			
Ivermectin (1% cream)‡	Once daily for 8 to 12 wk	Burning, skin irritation	High-quality evidence[1,22]
Azelaic acid (15% gel, 15% foam, or 20% cream)‡	Twice daily for 8 to 12 wk	Burning, stinging, skin irritation	Moderate-quality evidence[1,23]
Topical metronidazole (0.75% gel‡ or cream or 1% cream‡)	Twice daily for 8 to 12 wk	Pruritus, dry skin, skin irritation	Moderate-quality evidence[1,24-31]
Oral treatment for moderate-to-severe disease (to be combined with topical treatments)		All tetracyclines have similar side effects, with doxycycline (40 mg) having the fewest: gastrointestinal discomfort, photosensitivity, candidiasis	
Modified-release doxycycline‡¶	40 mg once daily for 8 to 12 wk		Moderate-quality evidence[1,32]
Tetracycline¶	250 to 500 mg (tapering) twice daily for 8 to 12 wk		Moderate-quality evidence[1,33,34]

Doxycycline¶	100 mg once daily for 8 to 12 wk		Low-quality evidence[1,35]
Oral treatment for severe disease			
Isotretinoin¶	0.25 to 0.30 mg per kilogram of body weight per day for 12 to 16 wk	Cheilitis, dry mouth and lips, epistaxis, myalgia, increased triglyceride level, increased alanine aminotransferase level, birth defects	High-quality evidence[1,36,37]
Phyma			
Inflamed			Observational studies[1,6,15-18]
Tretinoin (0.025% cream or 0.01% lotion)¶	Once or twice daily for 8 to 12 wk	Redness, dryness, itching, scaling, mild burning	
Oral doxycycline¶	100 mg once daily for 8 to 12 wk	Gastrointestinal discomfort, photosensitivity, candidiasis	
Oral tetracycline¶	250 to 500 mg (tapering) twice daily for 8 to 12 wk	Gastrointestinal discomfort, photosensitivity, candidiasis	
Oral isotretinoin¶	0.25 to 0.30 mg per kilogram per day for 3 to 4 mo	Cheilitis, dry mouth and lips, epistaxis, myalgia, increased triglyceride level, increased alanine aminotransferase level, birth defects	
Noninflamed			Observational studies[1,6,15-18]
Surgical interventions or ablative laser therapy	One or two treatments (electrosurgery, excision)	Pain, crusts, scarring	
Ocular rosacea			
Artificial tears	As needed, according to the patient's assessment	Blurred vision	Expert opinion[15-18]
Eyelid hygiene	Lukewarm water or warm compresses twice daily	No specific side effects	Expert opinion[15-18]
Cyclosporine (0.05% eyedrops)‡¶	One drop twice daily	Blurred vision, eye redness, eye pain, itching	Low-quality evidence[1,38]
Fusidic acid gel	Application on eyelid margin twice daily	Stinging, burning, eye soreness, blurred vision	Randomized, controlled trial[1]
Metronidazole (0.75% gel)	Application on eyelid margin twice daily	Itching, burning, blurred vision	Inconclusive evidence from one randomized, controlled trial[1] and some nonrandomized, controlled trials[6,16]
Modified-release oral doxycycline 40 mg¶ or 100 mg¶	40 mg or 100 mg once daily	Gastrointestinal discomfort, photosensitivity, candidiasis	Observational studies[39,40]

* Data are from van Zuuren et al.,[1] Elewski et al.,[6] Picardo et al.,[10] Two et al.,[11] Two et al.,[14] Schaller et al.,[15] Powell,[16] Reinholz et al.,[17] and Asai et al.[18] Nd:YAG denotes neodymium:yttrium–aluminum–garnet.

† In cases in which the quality of evidence was rated in the Cochrane review according to a grading system developed by the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) Working Group,[1,19] the rating is listed in the last column as high-quality evidence ("further research is very unlikely to change our confidence in the estimate of effect"), moderate-quality evidence ("further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate"), low-quality evidence ("further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate"), or very low-quality evidence ("we are very uncertain about the estimate"). GRADE is a systematic and explicit approach to making judgements about the quality of evidence and the strength of recommendations. In the Cochrane review, the quality of evidence was rated for the outcomes of only the interventions that were considered to be the most important, and studies other than randomized, controlled trials were not included in the Cochrane review.

‡ This treatment is approved by the Food and Drug Administration for this indication.

§ 0.5% brimonidine tartrate gel is equivalent to 0.33% of brimonidine free base.

¶ This treatment is contraindicated in pregnancy.

as assessed by both the patient and the physician.[1] One of these trials, which assessed the change from baseline in the number of inflammatory lesions, showed a markedly greater reduction in the number of lesions with azelaic acid than with vehicle (62% decrease vs. 47% decrease).[23] The efficacy of 0.75% metronidazole gel or cream twice daily or 1% metronidazole cream once or twice daily was investigated in eight randomized, controlled trials involving a total of 1964 patients, with trial durations that ranged from 8 weeks to 6 months.[24-31] The reduction in the number of lesions was consistently greater in the metronidazole groups than in the placebo groups, with reductions ranging from 58 to 78% in the metronidazole groups as compared with 46 to 48% in the placebo groups.[1] In a trial involving 757 participants in which 1% ivermectin once daily was compared with 0.75% metronidazole gel twice daily with respect to the rates of maintenance of remission after 16 weeks of treatment, participants who had been assigned to receive metronidazole had a slightly higher rate of relapse (as defined by the recurrence of at least a few inflammatory lesions) over a period of 36 weeks than participants in the ivermectin group (68% vs. 63%) and a shorter time to relapse (mean, 85 days vs. 115 days).[45] Other topical treatments that are sometimes prescribed include a combination of 10% sodium sulfacetamide and 5% sulfur in cream or lotion form twice daily, permethrin cream twice daily, and retinoids once daily, but the limited data to support the use of these treatments are from randomized trials of low methodologic quality.[1,6,14,16,17]

When first-line treatments are inadequate in mild cases or when rosacea is more severe at presentation, combining topical treatments with oral antibiotic agents is generally recommended, although supporting data are limited. The only oral treatment approved by both the FDA and the European Medicines Agency for inflammatory lesions associated with rosacea is modified-release doxycycline at a dose of 40 mg once daily. This dose is considered to have antiinflammatory effects but not an antimicrobial effect.[1] In two randomized, controlled trials involving a total of 537 patients, treatment with doxycycline at a dose of 40 mg resulted in significantly greater reductions in the number of lesions than those observed with placebo, with mean reductions of 46% and 61% in the doxycycline groups and mean reductions of 20% and 29% in the placebo groups.[1,32] A randomized, noninferiority trial that compared doxycycline at a dose of 40 mg with doxycycline at a dose of 100 mg showed that the two doses had similar efficacy, but substantially fewer adverse events (mainly gastrointestinal) were reported in the 40-mg group than in the 100-mg group.[1,35] Treatment with tetracycline has also been associated with significant reductions in the numbers of inflammatory lesions,[33,34] but such treatment tends to result in more marked gastrointestinal side effects (e.g., nausea and diarrhea) than treatment with doxycycline. Data are lacking to support the use of minocycline for rosacea, and in rare cases, minocycline has been reported to cause serious side effects, such as hyperpigmentation of the skin and tissues, autoimmune hepatitis, and lupus erythematosus.[17,18] In cases in which the use of tetracyclines either is contraindicated or has previously resulted in unacceptable side effects, azithromycin at a dose of 250 to 500 mg two to three times weekly, erythromycin at a dose of 250 to 500 mg once or twice daily, and clarithromycin at a dose of 250 mg every other day or daily can be considered, although the use of each of these medications is supported primarily by observational studies.[1,16,17]

For severe cases of inflammatory papules and pustules or for inflammatory papules and pustules that do not respond to oral antibiotics or that recur after the discontinuation of oral antibiotics, treatment with low-dose oral isotretinoin (0.25 to 0.30 mg per kilogram of body weight per day) for 12 to 16 weeks has been shown to be effective in two randomized, controlled trials.[1,36,37] In one of the trials,[36] isotretinoin was compared with doxycycline at a dose of 50 to 100 mg and showed a slightly greater reduction in the numbers of lesions with isotretinoin than with doxycycline (89% vs. 83%). In the other trial,[37] in which isotretinoin was compared with placebo, a 90% or greater reduction in the number of lesions was observed in 57% of the patients in the isotretinoin group as compared with 10% of the patients in the placebo group. Isotretinoin should not be used by women who are pregnant or who may potentially become pregnant, since isotretinoin is highly teratogenic. The prevention of pregnancy during treatment with isotretinoin is crucial, and management

includes routine pregnancy tests and the use of effective birth control.[1]

Treatments for Phyma

Randomized, controlled trials evaluating interventions for phyma are lacking. For clinically inflamed phyma, treatment with topical retinoids, oral doxycycline, oral tetracycline, or oral isotretinoin is recommended on the basis of clinical experience. However, in the case of phymas that appear noninflamed, are more fibrotic, and are otherwise quiescent, case series have shown marked improvement in appearance and fewer symptoms after ablative laser therapy or surgical therapies, and the results are long-lasting (Fig. 2D).[1,6,15-18]

Treatments for Ocular Rosacea

Ocular involvement occurs in up to three quarters of patients with rosacea but is often underdiagnosed and remains understudied.[2] Most guidelines advise eyelid hygiene twice daily with warm water and the use of artificial tears.[15-18] One small, randomized trial suggested that cyclosporine eyedrops improved quality of life, as measured on the Ocular Surface Disease Index, and also increased tear production (both of which were primary outcomes in the trial).[1,38] However, cyclosporine should not be used when there is active ocular infection. Other treatment options for which there are limited data are topical metronidazole or fusidic acid applied to the eyelids.[1,6] For patients who have more severe ocular involvement, observational data have suggested that the use of oral doxycycline at a dose of either 40 mg (modified-release formulation) or 100 mg can reduce symptoms.[6,15,17,18,39,40] If symptoms are not reduced, or in cases in which eyesight might be affected, referral to an ophthalmologist may be warranted to rule out other diagnoses, to monitor treatment, and to prevent rare complications, such as vision-threatening ocular disease (e.g., keratitis).[2,6,16,18]

Treatments for Pregnant or Lactating Women

Many interventions that are used for rosacea are unsuitable for women who are pregnant or lactating. Intense pulsed-light therapy and laser treatment are generally assumed to be safe, but such treatment is often deferred until after pregnancy because these procedures can be painful and distressing. For inflammatory lesions, 0.75% metronidazole gel or 1% metronidazole cream, azelaic acid (15% gel, 15% foam, or 20% cream), and 2% erythromycin gel or solution can be used.[16,46,47] The use of fusidic acid gel for ocular rosacea is permitted. For oral treatment, only macrolide antibiotics such as erythromycin, clarithromycin, and azithromycin have been recommended, but the use of tetracyclines and isotretinoin is absolutely contraindicated.[16,46,47]

Maintenance Therapy

Rosacea is a chronic condition, and although patients can have remissions, relapses commonly occur.[1,6,11,15,17,18] Therefore, patients typically receive maintenance therapy, although data on the effects of various therapies on remission rates are limited. Treatment with topical metronidazole, topical azelaic acid, and topical ivermectin has been shown to maintain remission after clearance of inflammatory lesions.[29,48] In one randomized trial (involving 88 participants) in which 0.75% metronidazole twice daily was compared with vehicle twice daily over the course of 6 months, the rate of relapse in the vehicle group was almost twice the rate in the metronidazole group (42% vs. 23%).[29] In two extension trials of 40 weeks' duration (involving a total of 1371 participants) in which 1% ivermectin cream once daily was compared with 15% azelaic acid gel twice daily,[48] adverse effects were uncommon but were less common with 1% ivermectin cream than with 15% azelaic acid gel, and the efficacy of ivermectin increased over time. In an open-label trial, brimonidine tartrate gel maintained efficacy with respect to a reduction in erythema over the course of 12 months.[49] For ocular rosacea, continued eyelid hygiene and the use of artificial tears are recommended.

AREAS OF UNCERTAINTY

The pathophysiology of this condition is incompletely understood.[1,9,12] Associations have been observed with a variety of chronic systemic conditions, such as cardiovascular diseases, metabolic disorders, autoimmune diseases, and Parkinson's disease, but these associations require confirmation and further study.[5,10,50,51] For some frequently prescribed treatments, such as topical benzoyl peroxide (either as monotherapy or com-

bined with topical antibiotics), topical retinoids, oral erythromycin, and azithromycin, randomized, controlled trials are either lacking or have not shown benefit. There is little high-quality evidence for the treatment of ocular rosacea. In clinical practice, various treatment options for rosacea (e.g., topical, oral, and sometimes light-based therapies) are often combined, but there is currently insufficient evidence to determine the efficacy and safety of these combinations. Further study is needed on maintenance therapies, as well as the time to response to the original treatment and the duration of the response.[1] The use of standardized and validated outcome measures would facilitate comparisons across trials and the synthesis of data in a meta-analysis.[1,52] A protocol for the development of a core set of outcomes to be evaluated in clinical trials of rosacea was published recently.[52] Given the known effects of rosacea on quality of life, more data are needed on patient-reported outcomes associated with various treatments.[1]

GUIDELINES

Guidelines for the treatment and management of rosacea have been published by the American Acne and Rosacea Society (https://acneandrosacea.org/guidelines/rosacea-medical-management-guidelines), the German Society of Dermatology,[17] and most recently, the Canadian Dermatology Association.[18] Furthermore, the international ROSCO panel recently published a consensus statement on rosacea treatment.[15] The suggested treatment strategy in the current article is in broad agreement with these guidelines.

CONCLUSIONS AND RECOMMENDATIONS

The woman described in the vignette has features of rosacea that include erythema, flushing, and inflammatory lesions. Rosacea encompasses a wide clinical spectrum, including erythema, telangiectasia, inflammatory papules and pustules, phymatous changes, and ocular features. Similar to the woman described in the vignette, patients frequently present with more than one phenotype associated with rosacea. Treatment should be based on presenting features and may include combination treatments. Management should include education about rosacea and advice regarding routine skin care (Table 1). I would recommend that the patient keep a diary to help identify triggers of her flushing, and I would suggest the use of nonirritating facial products and camouflage cosmetics, along with the use of a sunscreen with a sun protection factor of 30 or greater. Because the inflammatory lesions reportedly responded well to 0.75% metronidazole gel twice daily, it would be reasonable for the patient to restart the same regimen and to continue to follow the regimen for at least 8 to 12 weeks. Other effective first-line treatments for inflammatory lesions include topical azelaic acid twice daily or topical ivermectin once daily. To address the patient's erythema, application of brimonidine tartrate gel or oxymetazoline cream in the morning could also be considered. Follow-up is important to evaluate adherence to the therapy and to discuss the diary and the triggers that have been identified. Systemic therapies (e.g., doxycycline at a dose of 40 mg [modified-release formulation] or 100 mg) can be discussed as treatment options in combination with topical agents if the response to the topical agents alone is deemed by the physician, the patient, or both to be inadequate. Continuation of topical therapy after remission of rosacea is recommended to reduce the risk of recurrence.

Dr. van Zuuren reports receiving lecture fees, travel support, and meeting registration fees from Galderma. No other potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

I thank Professor Jerry Tan, Professor Zbys Fedorowicz, and Bernd Arents for their detailed review of the manuscript.

REFERENCES

1. van Zuuren EJ, Fedorowicz Z, Carter B, van der Linden MM, Charland L. Interventions for rosacea. Cochrane Database Syst Rev 2015;4:CD003262.
2. Vieira AC, Mannis MJ. Ocular rosacea: common and commonly missed. J Am Acad Dermatol 2013;69:Suppl 1:S36-S41.
3. Halioua B, Cribier B, Frey M, Tan J. Feelings of stigmatization in patients with rosacea. J Eur Acad Dermatol Venereol 2017;31:163-8.
4. Bewley A, Fowler J, Schöfer H, Kerrouche N, Rives V. Erythema of rosacea impairs quality of life: results of a meta-analysis. Dermatol Ther (Heidelb) 2016;6:237-47.
5. Egeberg A, Hansen PR, Gislason GH, Thyssen JP. Patients with rosacea have increased risk of depression and anxiety disorders: a Danish nationwide cohort study. Dermatology 2016;232:208-13.

6. Elewski BE, Draelos Z, Dréno B, Jansen T, Layton A, Picardo M. Rosacea — global diversity and optimized outcome: proposed international consensus from the Rosacea International Expert Group. J Eur Acad Dermatol Venereol 2011;25:188-200.

7. Tan J, Berg M. Rosacea: current state of epidemiology. J Am Acad Dermatol 2013;69:Suppl 1:S27-S35.

8. Wilkin J, Dahl M, Detmar 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;46:584-7.

9. Tan J, Almeida LM, Bewley A, et al. Updating the diagnosis, classification and assessment of rosacea: recommendations from the global ROSacea COnsensus (ROSCO) panel. Br J Dermatol 2017;176:431-8.

10. Picardo M, Eichenfield LF, Tan J. Acne and rosacea. Dermatol Ther (Heidelb) 2017;7:Suppl 1:43-52.

11. Two AM, Wu W, Gallo RL, Hata TR. Rosacea: part I. Introduction, categorization, histology, pathogenesis, and risk factors. J Am Acad Dermatol 2015;72:749-58.

12. Steinhoff M, Schauber J, Leyden JJ. New insights into rosacea pathophysiology: a review of recent findings. J Am Acad Dermatol 2013;69:Suppl 1:S15-S26.

13. Del Rosso JQ, Thiboutot D, Gallo R, et al. Consensus recommendations from the American Acne & Rosacea Society on the management of rosacea, part 1: a status report on the disease state, general measures, and adjunctive skin care. Cutis 2013;92:234-40.

14. Two AM, Wu W, Gallo RL, Hata TR. Rosacea: part II. Topical and systemic therapies in the treatment of rosacea. J Am Acad Dermatol 2015;72:761-70.

15. Schaller M, Almeida LM, Bewley A, et al. Rosacea treatment update: recommendations from the global ROSacea COnsensus (ROSCO) panel. Br J Dermatol 2017;176:465-71.

16. Powell FC. Rosacea. N Engl J Med 2005;352:793-803.

17. Reinholz M, Tietze JK, Kilian K, et al. Rosacea — S1 guideline. J Dtsch Dermatol Ges 2013;11:768-80.

18. Asai Y, Tan J, Baibergenova A, et al. Canadian clinical practice guidelines for rosacea. J Cutan Med Surg 2016;20:432-45.

19. Schünemann H, Brożek J, Guyatt G, Oxman A, eds. GRADE [Grading of Recommendations, Assessment, Development and Evaluation] handbook. October 2013 (http://www.guidelinedevelopment.org/handbook).

20. Fowler J Jr, Jackson M, Moore A, et al. Efficacy and safety of once-daily topical brimonidine tartrate gel 0.5% for the treatment of moderate to severe facial erythema of rosacea: results of two randomized, double-blind, and vehicle-controlled pivotal studies. J Drugs Dermatol 2013;12:650-6.

21. Rhofade cream prescribing information. Irvine, CA: Allergan, 2017 (https://www.allergan.com/assets/pdf/rhofade_pi.pdf).

22. Stein L, Kircik L, Fowler J, et al. Efficacy and safety of ivermectin 1% cream in treatment of papulopustular rosacea: results of two randomized, double-blind, vehicle-controlled pivotal studies. J Drugs Dermatol 2014;13:316-23.

23. Draelos ZD, Elewski B, Staedtler G, Havlickova B. Azelaic acid foam 15% in the treatment of papulopustular rosacea: a randomized, double-blind, vehicle-controlled study. Cutis 2013;92:306-17.

24. Beutner K, Calvarese B. A multi-center, investigator-blind clinical trial to assess the safety and efficacy of metronidazole gel 1% as compared to metronidazole gel vehicle and metronidazole cream 1% in the treatment of rosacea. J Am Acad Dermatol 2005;52(3):Suppl 10. abstract.

25. Bitar A, Bourgouin J, Doré N, et al. A double-blind randomised study of metronidazole (Flagyl) 1% cream in the treatment of acne rosacea. Drug Invest 1990;2:242-8.

26. Bjerke JR, Nyfors A, Austad J, et al. Metronidazole (Elyzol) 1% cream v. placebo cream in the treatment of rosacea. Clin Trials J 1989;26:187-94.

27. Bleicher PA, Charles JH, Sober AJ. Topical metronidazole therapy for rosacea. Arch Dermatol 1987;123:609-14.

28. Breneman DL, Stewart D, Hevia O, Hino PD, Drake LA. A double-blind, multicenter clinical trial comparing efficacy of once-daily metronidazole 1 percent cream to vehicle in patients with rosacea. Cutis 1998;61:44-7.

29. Dahl MV, Katz HI, Krueger GG, et al. Topical metronidazole maintains remissions of rosacea. Arch Dermatol 1998;134:679-83.

30. Koçak M, Yağli S, Vahapoğlu G, Ekşioğlu M. Permethrin 5% cream versus metronidazole 0.75% gel for the treatment of papulopustular rosacea: a randomized double-blind placebo-controlled study. Dermatology 2002;205:265-70.

31. Nielsen PG. Treatment of rosacea with 1% metronidazole cream: a double-blind study. Br J Dermatol 1983;108:327-32.

32. Del Rosso JQ, Webster GF, Jackson M, et al. Two randomized phase III clinical trials evaluating anti-inflammatory dose doxycycline (40-mg doxycycline, USP capsules) administered once daily for treatment of rosacea. J Am Acad Dermatol 2007;56:791-802.

33. Marks R, Ellis J. Comparative effectiveness of tetracycline and ampicillin in rosacea: a controlled trial. Lancet 1971;2:1049-52.

34. Sneddon IB. A clinical trial of tetracycline in rosacea. Br J Dermatol 1966;78:649-52.

35. Del Rosso JQ, Schlessinger J, Werschler P. Comparison of anti-inflammatory dose doxycycline versus doxycycline 100 mg in the treatment of rosacea. J Drugs Dermatol 2008;7:573-6.

36. Gollnick H, Blume-Peytavi U, Szabó EL, et al. Systemic isotretinoin in the treatment of rosacea — doxycycline- and placebo-controlled, randomized clinical study. J Dtsch Dermatol Ges 2010;8:505-15.

37. Sbidian E, Vicaut É, Chidiack H, et al. A randomized-controlled trial of oral low-dose isotretinoin for difficult-to-treat papulopustular rosacea. J Invest Dermatol 2016;136:1124-9.

38. Schechter BA, Katz RS, Friedman LS. Efficacy of topical cyclosporine for the treatment of ocular rosacea. Adv Ther 2009;26:651-9.

39. Sobolewska B, Doycheva D, Deuter C, Pfeffer I, Schaller M, Zierhut M. Treatment of ocular rosacea with once-daily low-dose doxycycline. Cornea 2014;33:257-60.

40. Quarterman MJ, Johnson DW, Abele DC, Lesher JL Jr, Hull DS, Davis LS. Ocular rosacea: signs, symptoms, and tear studies before and after treatment with doxycycline. Arch Dermatol 1997;133:49-54.

41. Tanghetti E, Del Rosso JQ, Thiboutot D, et al. Consensus recommendations from the American Acne & Rosacea Society on the management of rosacea, part 4: a status report on physical modalities and devices. Cutis 2014;93:71-6.

42. Bjerke R, Fyrand O, Graupe K. Double-blind comparison of azelaic acid 20% cream and its vehicle in treatment of papulo-pustular rosacea. Acta Derm Venereol 1999;79:456-9.

43. Carmichael AJ, Marks R, Graupe KA, Zaumseil RP. Topical azelaic acid in the treatment of rosacea. J Dermatolog Treat 1993;4:S19-S22.

44. Thiboutot D, Thieroff-Ekerdt R, Graupe K. Efficacy and safety of azelaic acid (15%) gel as a new treatment for papulopustular rosacea: results from two vehicle-controlled, randomized phase III studies. J Am Acad Dermatol 2003;48:836-45.

45. Taieb A, Khemis A, Ruzicka T, et al. Maintenance of remission following successful treatment of papulopustular rosacea with ivermectin 1% cream vs. metronidazole 0.75% cream: 36-week extension of the ATTRACT randomized study. J Eur Acad Dermatol Venereol 2016;30:829-36.

46. Bechstein SK, Ochsendorf F. Acne and rosacea in pregnancy. Hautarzt 2017;68:111-9. (In German.)

47. Tyler KH. Dermatologic therapy in pregnancy. Clin Obstet Gynecol 2015;58:112-8.

48. Stein Gold L, Kircik L, Fowler J, et al. Long-term safety of ivermectin 1% cream vs azelaic acid 15% gel in treating inflammatory lesions of rosacea: results of two 40-week controlled, investigator-blinded trials. J Drugs Dermatol 2014;13:1380-6.
49. Moore A, Kempers S, Murakawa G, et al. Long-term safety and efficacy of once-daily topical brimonidine tartrate gel 0.5% for the treatment of moderate to severe facial erythema of rosacea: results of a 1-year open-label study. J Drugs Dermatol 2014;13:56-61.
50. Rainer BM, Fischer AH, Luz Felipe da Silva D, Kang S, Chien AL. Rosacea is associated with chronic systemic diseases in a skin severity-dependent manner: results of a case-control study. J Am Acad Dermatol 2015;73:604-8.
51. Egeberg A, Hansen PR, Gislason GH, Thyssen JP. Exploring the association between rosacea and Parkinson disease: a Danish nationwide cohort study. JAMA Neurol 2016;73:529-34.
52. Iyengar S, Williamson PR, Schmitt J, et al. Development of a core outcome set for clinical trials in rosacea: study protocol for a systematic review of the literature and identification of a core outcome set using a Delphi survey. Trials 2016;17:429.