Cutaneous rosacea: a thorough overview of pathogenesis, clinical presentations, and current recommendations on management

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The review summarizes and systemizes available international data on the pathogenesis, clinical manifestations and current recommendations for the management of rosacea patients.

Key words: **rosacea, pathophysiological mechanisms, clinical manifestations, exacerbations of rosacea and possible triggers, recommendations for a drug therapy, 0.5% brimonidine tartrate gel, 1% ivermectin cream.**

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Rosacea is a common inflammatory disorder that affects both genders and most commonly presents on the central face [1]. The prevalence of rosacea has been estimated in epidemiologic studies from selected populations; suffice it is to say that it is a very common disorder that presents regularly in dermatology and primary care clinics [1]. Although reported to most commonly affect individuals with facial skin rated as Fitzpatrick Skin Type I-II, rosacea can affect people of any race, skin color, and creed. The published frequency of rosacea derived from patient visit data collected over a fifteen year period at a large practice in the United Kingdom reported an incidence of 1.65 per 1000 person-years, with patients >30 years of age representing over 80% of the rosacea cases that were encountered [3].

Clinical Manifestations of Rosacea

Rosacea usually manifests clinically in the third to fourth decade of life. The earliest feature is often characterized to be a transient "flushing" which reflects an acute-subacute vasodilation of central facial vasculature that subsides without any other visible features of rosacea, thus confounding the ability to diagnose the disorder at this early time point. The usual clinical course of rosacea is typified by periods of exacerbation of visible signs and symptoms followed by variable durations of remission. Over time, there are clinical manifestations of rosacea that are present during flares and some that persist between flares, thus making it easier to make a correct diagnosis of rosacea. The clinical presentations of rosacea and its clinical course vary from patient to patient and may change over time [2, 4-7].

It is important for the clinician to appreciate and differentiate that some clinical facial manifestations of rosacea are intermittent (transient), occurring during a rosacea flare, and others are permanent (non-transient), present both during and between flares (Figure 1). The visible features of rosacea that are present intermittently (i.e. during a flare) are increased central facial erythema due to vascular dilatation (flushing of rosacea) that oc-

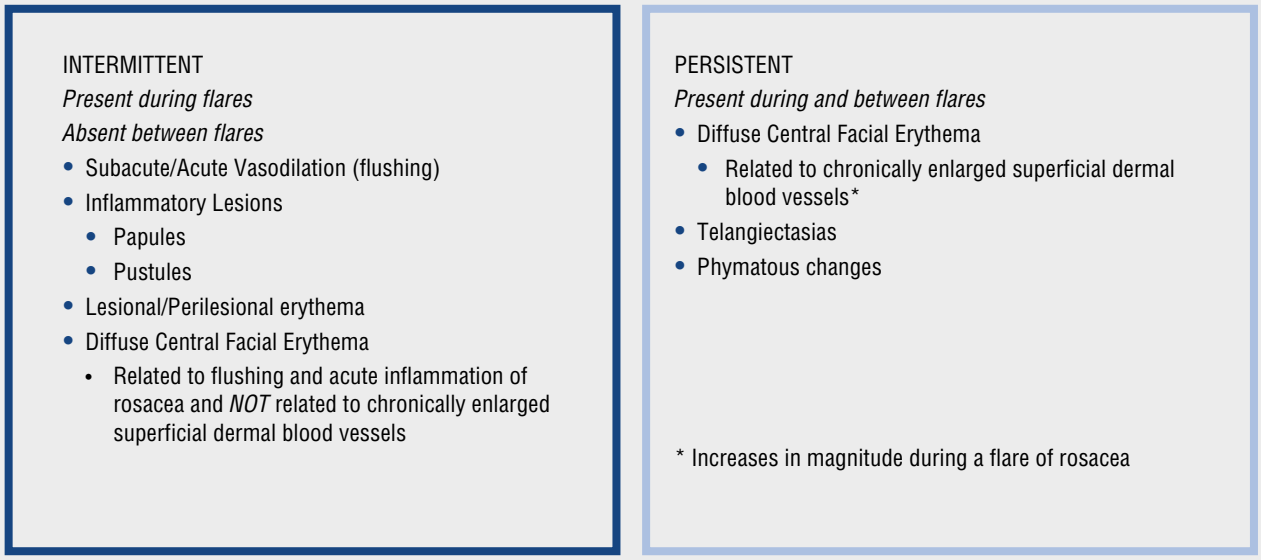


Figure 1. Clinical Manifestations of Cutaneous Rosacea

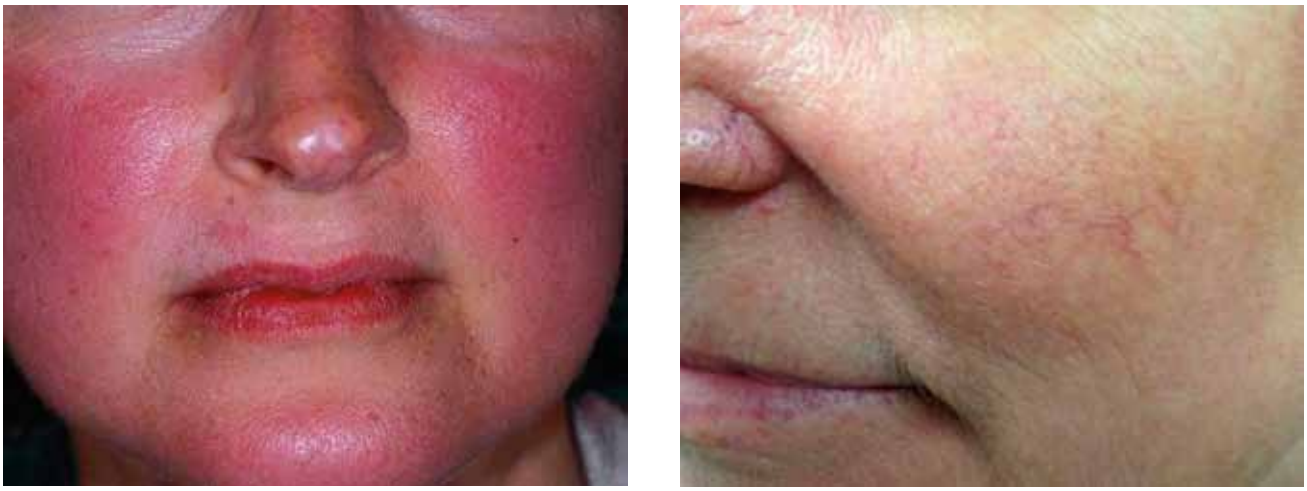
curs in the vast majority of patients, and papulopustular lesions, that occur on the inner cheeks, central forehead and/or chin in a defined subset of patients [1, 2, 4-9]. Papules and pustules are often described as the inflammatory lesions of rosacea, and when present as visible findings, they are intermittent, as they emerge during a rosacea flare and resolve as the rosacea flare dissipates [1, 2, 4-6]. The predominant permanent visible manifestation that persist between flares is non-transient central facial erythema, referred to as background erythema, that is diffuse, macular, usually confluent, and sometimes associated with soft edema, and associated facial telangiectasias, that are linear, and often very fine in appearance, or some can individually be thicker and more defined (Figure 2) [2, 4-9]. Phymatous proliferations, which represent confluent sebaceous hyperplasia sometimes with mucinous and fibrous changes, occur most often on the nose (rhinophyma), are permanent findings [2, 4, 7].

The visible patterns of rosacea have been defined as subtypes to differentiate clinically with correlations of subset presentations to approaches to management [2, 4-6, 10]. The frequency of rosacea patients with central facial erythema only, which is designated as erythematotelangiectatic rosacea (subtype 1), is reported to be four-fold higher compared to patients presenting with papulopustular rosacea (subtype 2) [1, 2, 4]. Phymas have been estimated to affect from 1-4% of individuals with rosacea, and are seen more often in men [1, 2, 4-7].

Clinical Course of Rosacea and Current Rosacea Assessment

At its initial onset, rosacea commonly presents as transient bouts of central facial flushing caused by vasodilation and increased blood flow which is most dominant on the central face [2, 4, 7-9]. As described above, after the vasodilation that causes the flushing resolves, the facial skin visibly appears normal [4-8]. As bouts of central facial flushing repeatedly exacerbate and remit over time, the facial vasculature progressively becomes dilated and enlarged and also proliferates, leading to the emergence of non-transient background erythema and telangiectasias; both background erythema and telangiectasias are present between flares and persist between the flares [2, 5, 6-10].

Ultimately, the optimal management of rosacea warrants the static evaluation of the visible manifestations that are present in the individual patient at a given point in time [1, 5, 6, 10]. At the time of presentation, the current assessment of rosacea depends on (1) if the condition is flared or in remission; (2) if papulopustular lesions are present during a flare; (3) if phymatous changes are present; (4) the visible intensity of background erythema; (5) the magnitude, size, and pattern of telangiectasias; (6) if rosacea dermatitis is clinically apparent; and (7) if associated symptomatology is present (discussed below). As increased central facial transepidermal water loss (TEWL) and decreased stratum corneum water content (hydration) have been shown to be present in rosacea, especially during a flare, visible pink erythema and diffuse fine facial



a *b*

Figure 2. Background facial erythema of rosacea: *a* — persistent, non-transient with predominance of diffuse central facial erythema; telangiectasias present; *b* — persistent, non-transient with predominance of telangiectasias and mild diffuse central facial erythema

scaling may be noted, and has been described as rosacea dermatitis [5, 6, 10, 11].

As referred to earlier, rosacea has been classified using subtype designations that were published in 2002 [4]. A series of more recent publications from the American Acne & Rosacea Society have stressed the clinical relevance of defining the visible manifestations in the individual patient at the time of presentation. This allows for selection of a therapeutic approach that is targeted to treat the manifestations that are present in that patient, and not based solely on a irrespective of a subtype category [6, 10, 13]. The two most commonly encountered presentations of rosacea are diffuse central facial erythema without papulopustular lesions and diffuse central facial erythema with papulopustular lesions (Figure 3) [1, 2, 5, 6, 13]. Phymatous changes and/or ocular manifestations of rosacea can occur concurrently in patients with any presentation of rosacea [1, 2, 4, 5, 6, 7, 10, 13].

Symptomatology Associated With Rosacea

Episodic flushing during a rosacea flare is often associated with symptomatology. This includes a sensation of facial warmth. Symptoms of increased facial skin sensitivity, such as stinging, burning, tingling and pruritus are common, including when facial skin is contacted by several products commonly used for skin care and personal hygiene [1, 2, 4-12]. Symptoms of skin sensitivity are more common and more severe during a rosacea flare, but may also be present between flares in rosacea-prone skin [2, 5, 6, 10].

Rosacea Flares and Possible Triggers

The natural disease course of rosacea has not been well studied, yet it is known that rosacea-affected individuals experience episodic exacerbations that are characterized by specific clinical features. These are the following: (1) flushing of rosacea with increased facial erythema due to dilation of central facial vasculature; (2) augmented inflammation which translates visibly to increased facial erythema; (3) soft central facial edema of variable magnitude; and (4) papulopustular lesions in some patients. Some of the triggers that have been noted to induce rosacea flares are ambient heat, hot liquids which cause oral-thermal flushing, spicy foods, and vasodilatory ingestants such as alcohol (e.g. red wine) and niacin [1, 2, 5-8, 10, 14-18]. Although not a mandatory pathogenic component of rosacea, proliferation of Demodex mites can serve as a trigger in some rosacea-prone patients through stimulation of specific inflammatory pathways [5, 19, 20]. Neurogenic, immunologic, and inflammatory pathways have been identified that appear to be operative in rosacea pathophysiology; physiochemical and structural difference in rosacea-affected skin as compared to normal skin have been reported [5, 6, 15-18, 21-25].

Pathophysiologic Mechanisms in Rosacea and Clinical Relevance

Publications devoted primarily to pathophysiology of rosacea appear elsewhere in the medical literature; nevertheless, explanations of rosacea-prone skin and the basic pathophysiologic mechanisms that seem to be operative in rosacea are necessary in order to better understand the direct correlations with specific signs and symptoms of rosacea and allow for more rational selection of individual therapies in each case that address specific clinical manifestations of rosacea [5, 6, 13, 22, 26-32]. Rosacea-prone skin is characterized by three major

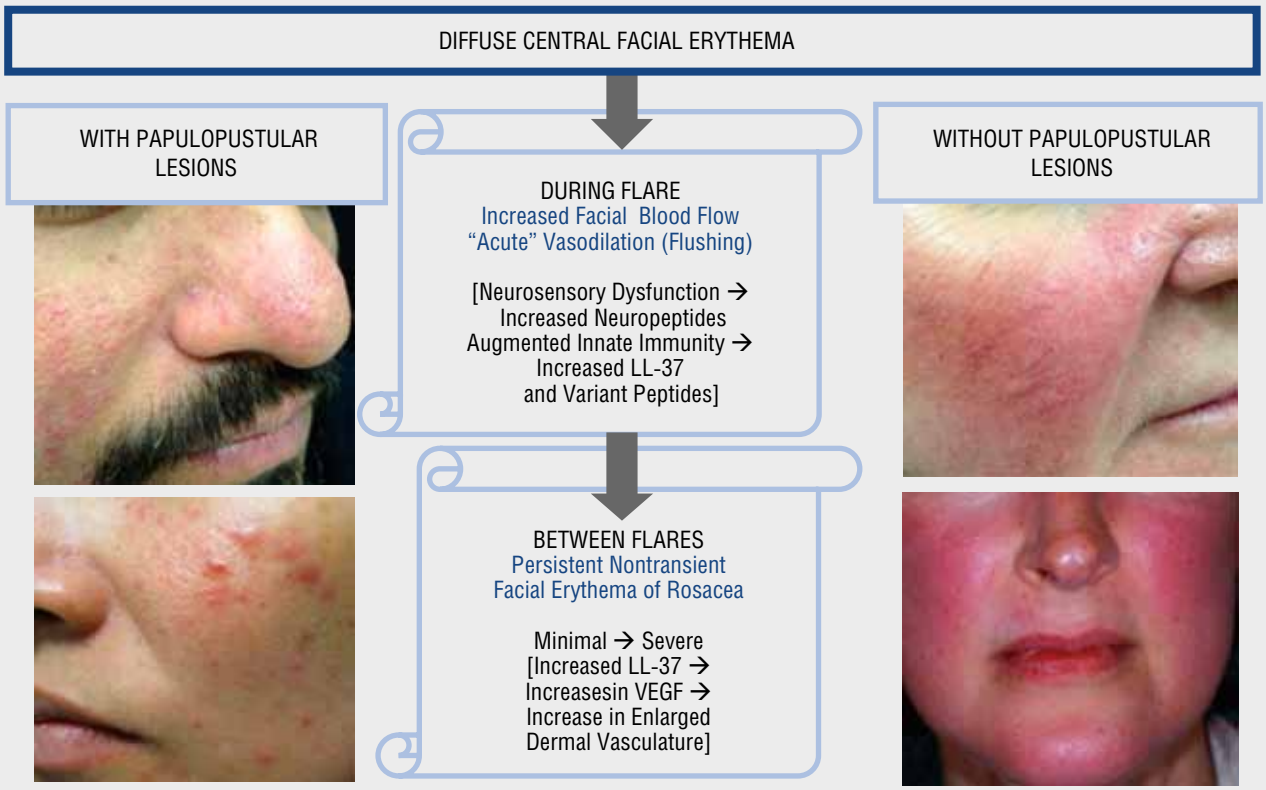


Figure 3. Common clinical presentations of cutaneous rosacea

inherent components: (1) neurovascular dysregulation; (2) augmented immune detection and response; and (3) several physiochemical alterations that identified in the facial skin of rosacea-affected individuals as compared to normal facial skin of individuals without rosacea [5, 6, 15-17, 33]. Essentially, rosacea-prone facial skin is "wired" to react to inciting factors that do not usually trigger an immunologic and/or inflammatory response in those without rosacea. Trigger that are recognized to induce rosacea flares (e.g. heat, UV light, spices) induce several reactions in rosacea-prone skin. These include neurogenic responses that cause vasodilation (flushing) and sensitive skin symptoms (stinging, burning, tingling) and cascade upregulation that increases antimicrobial peptide production (especially cathelicidin (LL-37) and other variant pro-inflammatory peptides) that induce cutaneous inflammation and vasodilation during the flare; repeated episodes of cathelicidin production are also believed to increase the density and diameter of superficial vasculature of central facial skin which progressively leads to non-transient facial erythema that is persistent between rosacea flares [2, 5-6, 8-10, 15-18, 21-28, 33]. Current information related to the potential modes of action of specific therapies used to treat specific clinical features of rosacea appear to at least partially explain why certain therapeutic agents improve some visible signs of rosacea and not others [2, 5, 6, 10, 13, 26, 29, 31-35].

Conventional Medical Management of Rosacea

The majority of studies of medical therapies for rosacea evaluate subjects with papulopustular lesions as a primary parameter, and also assess the associated lesional and perilesional erythema secondarily. To add, other than studies and reports with topical alpha-adrenergic agonists (e.g. bromonidine, oxymetazoline), none of the commonly used topical or oral therapies have demonstrated efficacy for the background non-transient facial erythema that persists between flares [5, 6, 9, 13, 26, 31-33, 36-38].

As no bacterium or microbe has been shown to be mandatory in the pathogenesis of rosacea, therapies which inhibit inflammatory pathways involved in rosacea have been central to therapy for papulopustular rosacea [2, 5, 6, 15-18, 21, 22, 27, 28, 39].

Proper Skin Care for Rosacea

Although skin care products and methodology are not controlled in many rosacea studies, proper skin care is an integral part of the rosacea management plan for several reasons [10-13, 35-38]. To summarize, using a properly selected gentle cleanser and moisturizer counteracts permeability barrier impairment when lessens signs and symptoms of facial skin irritation inherent to the disease or related to topical products applied to the skin. Photoprotection is also very important in the management of rosacea, as ambient heat and ultraviolet light are rosacea triggers, and chronic photodamage independently induces persistent erythema and telangiectasia in chronically exposed skin [1, 2, 5, 10-13, 16, 18-35].

Overview of Topical Agents for Rosacea

The most commonly used topical agents in the United States which are approved by the Food & Drug Administration (FDA) for papulopustular rosacea are metronidazole (Metro; 0.75% gel, cream, lotion; 1%; gel, cream), azelaic acid 15% (AzA; gel, foam), and ivermectin 1% cream (IVM) [31, 32, 36-38]. In papulopustular rosacea, these agents have been shown to significantly decrease papules, pustules, and lesional/perilesional erythema, the latter resolving as the papulopustular lesions remit.

The mechanism of action of topical metronidazole in rosacea is unknown. Mechanisms which can reduce inflammation in rosacea have been suggested but data are limited [31, 32, 37, 38]. Research data, including studies completed in subjects with papulopustular rosacea demonstrate that AzA reduces serine protease activity in rosacea-affected central facial skin which leads to decreased cathelicidin (LL-37) production and reduction in inflammation [34, 41].

Although reported to be of benefit in some small studies and case reports, less clinical and basic science research data are available with other topical agents that have been used for rosacea, such as sulfacetamide 10%-sulfur 5% formulations, calcineurin inhibitors, and permethrin [5, 13, 29, 31, 32, 36-38].

Overview of Oral Agents for Rosacea

The predominant oral therapeutic class that has been used for rosacea has been the tetracyclines, primarily oxytetracycline, tetracycline, and doxycycline utilized for treatment of papulopustular rosacea [31, 32, 36-38, 42]. Other oral antibiotics that have demonstrated efficacy for papulopustular rosacea include metronidazole and azithromycin [31, 32, 36, 38, 42-44]. Interestingly, oral antibiotics have been used to treat rosacea for over five decades despite the lack of definitive evidence that a bacterium is a causative or mandatory component of the pathogenesis of rosacea [2, 6, 16, 18, 21, 22, 30, 39].

It is believed that the biologic anti-inflammatory properties of tetracyclines that are unrelated to antibiotic activity are the major reason why these agents are of therapeutic benefit for rosacea [30, 34, 45-47]. This concept is further supported by several studies which demonstrate the effectiveness of subantimicrobial dose doxycycline (e.g. doxycycline hyclate 40 mg modified-release [MR] capsule once daily) in the treatment of papulopustular rosacea [30, 42, 48-51]. Subantimicrobial dose doxycycline exhibits a pharmacokinetic profile that is devoid of antibiotic selection pressure, but retains anti-inflammatory activity including downregulation of the cathelicidin pathway, thus circumventing alteration of the host microbiome and the antibiotic resistance that are inevitable with oral antibiotic therapy [42, 48-52]. In the phase III pivotal trials completed with doxycycline MR 40 mg capsule once daily versus placebo, no cases of vaginal candidiasis or photosensitivity were observed in the active treatment group [50]. Doxycycline MR 40 mg capsule once daily has demonstrated efficacy equivalent to doxycycline 100 mg daily for papulopustular rosacea, with a significantly lower incidence of gastrointestinal side effects [48]. Doxycycline 20 mg twice daily is also subantimicrobial, however, data are limited for treatment of rosacea, and anti-inflammatory activity is likely to be inadequate if there is incomplete adherence with twice daily use [42, 49, 52].

Oral isotretinoin may be effective in selected cases of recalcitrant papulopustular rosacea or in early phyma formation that has not progressed to a mucinous or fibrotic phase [39, 42, 53]. Unlike acne vulgaris, prolonged remissions of rosacea do not occur after isotretinoin is discontinued.

More Recent Additions to the Medical Therapy Armamentarium for Rosacea

Two topical therapies for rosacea that incorporate new active ingredients have emerged over the past three years. The first, brimoninide tartrate 0.5% (brimonidine 0.33%) gel is the first FDA-approved for treatment of persistent nontransient facial erythema of rosacea (background erythema). The second, ivermectin 1% cream, is indicated for treatment of papulopustular rosacea.

The Rationale for Topical α-Adrenergic Receptor Agonist Therapy in Rosacea

Central facial erythema that increases in visible intensity during flares and persists between flares is the primary diagnostic clinical feature of rosacea [2, 4, 5, 7, 14, 21, 26]. The increased intensity of erythema occurring during a flare reflects primarily vasodilation (flushing of rosacea). Importantly, multiple other processes contribute such as neurogenic inflammation, innate and acquired immunologic inflammation, lesional and perilesional erythema if papulopustular lesions are present, and epidermal permeability barrier impairment causing increased TEWL [2, 5, 6, 8, 11, 14-18, 21-28, 33]. However, the background erythema present between flares of rosacea correlates with the increased density and size of superficial dermal vasculature that remains physiologically vasoactive via sympathetic neural control,

and the presence of telangiectasias which are not vasoactive [2, 5, 6, 9, 14, 16, 18, 21, 26, 33, 54, 55].

Topically applied α-adrenergic receptor agonists (α-agonist) are the first class of topical agents shown to decrease the background facial erythema of rosacea. Brimonidine tartrate has been evaluated most extensively, with oxymetazoline and xylometazoline also discussed in case reports [33, 37, 56-58]. The therapeutic target of an α-agonist are the α-adrenoreceptors present in the smooth muscle layer encasing the wall of superficial dermal blood vessels. These vessels function physiologically to modulate vascular tone and relative blood flow within the superficial and deep plexuses of skin [26, 33]. The vasoconstriction that occurs after facial application of an α-agonist leads to reduction in erythema which persists over the duration of adequate binding with the α-adrenoreceptors in the vessel walls. Smaller papillary vessels such capillaries and telangiectasias do not vasoconstrict as they do not contain a fully formed smooth muscle sheath and hence, are not modulated by α-adrenergic control [26, 33, 56-58].

Topical Brimonidine for Non-Transient Erythema of Rosacea

Brimonidine tartrate (BT) is an α-agonist with selectivity for α_{-2}-adrenergic receptors [57]. A single application dose ranging study (n = 122) demonstrated that BT 0.5% gel (equivalent to brimonidine 0.33%) applied once daily exhibited the greatest effect on erythema reduction [57]. Pharmacokinetic analysis after application of BT gel to facial skin over 29 days compared to ocular application of BT 0.2% ophthalmic solution (used for open-angle glaucoma) showed a superior safety profile for BT 0.5% gel with low systemic exposure and no systemic drug accumulation observed over the course of the study [59]. The phase III pivotal trials evaluated adults (n = 553) with background erythema of rosacea and a maximum of two papulopustular lesions, with results consistent with those reported from a similarly designed phase II study (n = 269). Study outcomes demonstrated efficacy, favorable tolerability, a lack of systemic safety signals, absence of tachyphylaxis, and minimal potential for rebound with patients assessed at two weeks post-therapy [57, 60]. A 52-week open label, multicenter, evaluated BT 0.5% gel applied once daily in subjects with facial erythema of rosacea (n = 449) both with and without papulopustular lesions, with 29.2% of patients using concomitant topical (i.e. metronidazole, azelaic acid) or oral (i.e. tetracyclines) medications [61]. The long term data demonstrated that the efficacy of BT 0.5 gel sustained over the duration of the study and that tolerability and safety was consistent with data from the phase II and phase III trials.

Data from available studies demonstrate overall that BT 0.5% gel induces its onset of erythema reduction as early as 30 minutes, a peak effect at approximately 3 hours, and a duration of peak erythema reduction of approximately 6 hours after a single application. As the peak effect wanes, the usual pattern of reappearance of erythema was a progressive return of facial erythema over 2 to 3 hours to a level that was slightly less than baseline, however, in some cases the intensity of erythema can exceed what was noted at baseline before application or a paradoxical increase in erythema may be observed occasionally in some patients [57, 60]. Neither tachyphylaxis or worsening of papulopustular rosacea were observed in the long term study which included 335 subjects and 279 subjects treated with BT 0.5% gel once daily for 6 months and 12 months, respectively [61].

Safety assessments completed during the pivotal and long term studies with facial application of various concentrations of BT gel support an overall favorable safety profile with no systemic safety signals. BT 0.5% gel applied once daily for up to 52 weeks was associated with a cutaneous adverse event noted at some time in 105 subjects (23.4%), with worsening of erythema or rosacea, skin burning sensation, skin irritation, pruritus, flushing, and allergic dermatitis reported in 10.1%, 3.3%, 3.1%, 2.0%, 8.9%, and 1.6% of subjects, respectively.61 BT 0.5% gel was discontinued in 12.7% of subjects (n = 57) due to a cutaneous adverse event, which is not unexpected given the inherent vascular reactivity and skin sensitivity of rosacea and the potential for contact dermatitis in some patients. Sporadic cases of rebound erythema or paradoxical erythema with use of BT 0.5% gel have been published, most likely due to interpatient variability in vascular reactivity or confounding effects of exogenous rosacea triggers [62, 63]. It is recommended that clinicians and their staff inform patients that an increase in facial redness may sometimes occur, and to use BT 0.5% gel only how it is recommended.

Oxymetazoline, another α-agonist, is currently under research development in the US.

Topical Ivermectin for Papulopustular Rosacea

Ivermectin (IVM) is a semisynthetic endectocide that is from the avermectin family of compounds. For over two decades, IVM has been utilized orally to treat a variety of endoparasitic infestations, and both orally and topically to treat exoparasitic infestations [64]. The antiparasitic activity of IVM is through blockade of specific channels involved in neural synapse transmission found in invertebrates (e.g. worms, mites, lice) that can infest mammals, including humans [62]. Oral administration of IVM has been reported to be effective for demodecidosis, and in patients with cutaneous and ocular findings related to Demodex folliculorum proliferation [65, 66]. An increased density of facial D folliculorum has been demonstrated in some patients with both erythematotelangiectatic or papulopustular rosacea compared to facial skin of healthy controls, leading to studies of IVM cream in subjects with papulopustular rosacea [19, 20, 67]. As anti-inflammatory properties have been reported with IVM, the therapeutic activity of IVM may be related at least partially to these effects as Demodex proliferation is not present in all cases of rosacea [67].

IVM 1% cream applied once daily was shown to be superior to vehicle cream once daily in subjects with moderate to severe papulopustular rosacea in two randomized, controlled, pivotal trials (n = 1371). The mean inflammatory lesion count at baseline in the two studies were 30.9 (+/- 14.33) and 32.9 (+/- 13.70), which are markedly higher than baseline mean inflammatory lesion counts in studies of other FDA-approved drugs used to treat papulopustular rosacea.67 In both studies, a greater percentage of subjects in the IVM 1% group achieved “treatment success”, defined as “clear” or “almost clear”, based on investigator global assessment, with outcomes of 38.4% and 40.1% , and 11.6% and 18.8%, in the IVM study arms and the vehicle study arms, respectively (both $p < 0.01$). Inflammatory lesion count reductions compared to baseline was 76.0% and 75.0% in both IVM groups vs 50.0% for both vehicle groups, respectively, which was also significant [67]. The efficacy, safety, and tolerability assessments in pivotal and long term trials demonstrated the effectiveness of IVM 1% cream, with a low incidence of cutaneous application site reactions (e.g. burning, pruritus; no serious adverse events, no significant systemic side effects, and absence of clinically significant laboratory abnormalities [67, 68]. A randomized controlled study of IVM 1% cream once daily (n = 478) versus Metro 0.75% cream twice daily (n = 484) for papulopustular rosacea demonstrated the superior efficacy of IVM 1% in reducing inflammatory lesions as early as week 3 and by investigator global assessments evaluating treatment success ($p < 0.001$ for both) [69]. Additionally, remission of rosacea after discontinuation of therapy lasted approximately 4 weeks longer with IVM 1% as compared to Metro 0.75% cream [69].

Rosacea Management Recommendations: From the Benchtop to the Treatment Room

The following points summarize management recommendations based on the above review and supporting references, designed to optimize medical treatment of the more common clinical presentations of rosacea: central facial erythema with papulopustular lesions (papulopustular presentation) and central facial erythema without papulopustular lesions (erythematotelangiectatic presentation).

- The first step in optimal management of rosacea after obtaining pertinent details of the patient’s history, is to assess the current visible and symptomatic manifestations that are present.
- Control of the selection of skin care products and how they are integrated into the treatment regimen by the clinician is very important in all cases of rosacea. This supports use by the patient of a gentle cleanser and moisturizer which serves to reduce TEWL and symptoms of skin sensitivity, and decreases the potential for skin tolerability reactions related to medications and other products applied to rosacea-affected facial skin [2, 6, 10-13, 21, 31, 32, 39].
- As best as is possible from a practical perspective, avoidance of known rosacea triggers is strongly recommended in the management of rosacea [1, 2, 4, 5, 6, 31, 32, 39].
- Photoprotection, including avoidance of direct sunlight exposure as much as possible (especially during peak hours), and use of broad-spectrum sunscreen is strongly recommended. Avoidance of direct sunlight exposure and sunscreen use lessen the potential triggering effect of ultraviolet light on rosacea-prone facial skin. Avoidance of direct sunlight exposure, especially during peak hours, decreases the intensity of ambient heat which could otherwise serve as trigger for rosacea [1, 2, 6, 10-13, 31, 32].
- In patients with papulopustular rosacea, topical therapy, oral therapy, or a combination of both may be used, depending on severity.
  - If the papulopustular rosacea is mild to moderate in severity, topical therapy (e.g. Metro, IVM, AzA) alone is usually very effective in reducing inflammatory lesions and their associated erythema. Oral therapy with a tetracycline agent can also be used, with subantimicrobial dose doxycycline offering the major advantage of efficacy without emergence of antibiotic resistant bacteria [13, 31, 36, 37, 39, 42, 48-51].
  - For papulopustular rosacea rated in severity as moderate to severe, a combination of topical and oral therapy is commonly used to achieve control, usually followed within a few months (e.g. 2-3 months) by transition to topical therapy alone to continue the suppression of rosacea and reduce the frequency and severity of rosacea flares. Alternatively, the pivotal trials and other studies of subantimicrobial dose doxycycline were completed as monotherapy, supporting its use over a longer duration when transcending off of initial combination therapy. If it is elected to utilize topical therapy alone for papulopustular rosacea that is within the higher range of moderate severity or is graded as severe, IVM 1% cream was studied in subjects with a higher baseline mean inflammatory lesion count (approximately 30 lesions) than other agents for papulopustular rosacea (approximately 18 to 21 lesions) [31, 36, 37, 42, 48-51, 67, 70].
  - Once a flare of papulopustular rosacea is controlled, background erythema which is non-transient and persistent often becomes more evident. Background erythema may be treated by the addition of an α-agonist such as BT 0.5% gel once daily. It is important that gentle skin care and photoprotection be continued and that triggers be avoided. Telangiectasias that are bothersome to the patient may be treated with the appropriate laser and/or light modalities [13, 26, 33, 35, 37, 42, 57-61].

— If topical α-agonist therapy is initiated for papulopustular rosacea before therapy is given to reduce inflammatory lesions, background erythema will dissipate, but lesional-perilesional erythema will initially persist as small red dots until the inflammatory lesions resolve [33, 37].
— Oral isotretinoin is reserved for selected cases of recalcitrant papulopustular rosacea. Once controlled, low dose and intermittent dose regimens may be effective for long term management. Teratogenicity and potential side effects of oral isotretinoin therapy must be taken into consideration both before and during use [42, 53].

- Central facial erythema without papulopustular lesions may be managed medically by proper skin care, photoprotection, and application of an α-agonist, such as BT 0.5% gel. Physical modalities such as lasers (e.g. pulse dye laser [PDL]) and intense pulse light (IPL) can also be used for treatment of vascular erythema and telangiectasias. Oral agents have not been shown to be effective for persistent background erythema of rosacea [13, 26, 33, 35, 37, 42, 57-63].
- Fully developed phymas require surgical intervention. Early phymatous changes may respond to oral isotretinoin therapy [31, 35, 39].
- Although the focus of this article is cutaneous rosacea, ocular rosacea is responsive to therapy with an oral tetracycline, especially oral doxycycline. Ophthalmologic consultation is clearly warranted if vision is impaired, if associated symptomatology is severe, or if refractory to oral tetracycline therapeutic or other therapeutic measures [31, 32, 39, 42].

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Conflicts of interest

The author does not have any potential conflicts of interest requiring disclosure in this article