Review: Clinical Trial Outcomes

CLINICAL INVESTIGATION

Rosacea: advances in understanding pathogenesis and treatment

Clin. Invest. (2011) 1(5), 739–755

Lisa E Maier
Department of Dermatology, University of Michigan, 1910 Taubman Center, Box 0314 1500 E. Medical Center Dr., Ann Arbor, MI 48109, USA
and
VA Ann Arbor Health Care System, Ann Arbor, MI, USA
Tel.: +1 734 936 4192
Fax: +1 734 936 6395
E-mail: maierl@med.umich.edu

Rosacea is a common, chronic inflammatory skin disease that primarily affects the face. There is a wide range of clinical features in rosacea including persistent erythema, facial flushing, telangiectasia, inflammatory papules and phymas. The National Rosacea Society Expert Committee has identified four major subtypes of rosacea based on groups of these symptoms: erythematotelangiectatic rosacea, papulopustular rosacea, phymatous rosacea and ocular rosacea. The pathophysiology of rosacea has not been completely elucidated; however, recent research into this disorder has identified several potential etiologic agents and processes that contribute to the disease. The synthesis of this research allows us to begin to understand how our current therapies work and provides us potential targets for future therapies. This article will review our current theories of rosacea pathogenesis, outline treatment options and discuss avenues for future research.

Keywords: demodex • innate immunity • pathogenesis • rosacea • treatment

Rosacea is a common and chronic inflammatory disease of the skin that predominantly affects the face. It is a disease of widely varying clinical features that range from facial erythema, flushing, papules and pustules to the disfiguring tissue hypertrophy of phymas. The National Rosacea Society (NRS) estimates that greater than 16 million Americans have this disease [201]. In Germany the prevalence has been estimated at approximately 2% [1]. In Sweden it has been estimated at 10% [2], 14.4% in Ireland [201] and 22% in Estonia [3]. This varying prevalence may be due to differences in classification criteria, sampling and possibly genetic background. It has been reported that light skin appears more susceptible; however, rosacea certainly occurs in darker skin types [4]. A study from Tunisia, where the population has primarily darker skin phototypes, found a rosacea prevalence of 0.2% in a cohort of dermatology oupatients [5]. Both men and women are affected by rosacea [6]. Rosacea generally affects adults much more than children, but there are pediatric forms. Children with rosacea often have similar features as seen in adults, such as flushing, telangiectasia, papules, pustules and eye involvement. Phymatous changes, however, have not been reported [7].

Rosacea is a disease with significant morbidity. Patients describe physical discomfort such as stinging, flushing, cosmetic intolerance and ocular irritation. Many also suffer from the emotional consequences of the disease. The patient may feel disfigured because of phymas or even from the persistent redness and acneiform lesions. It can be socially stigmatizing because of the common misperception that only heavy drinkers get rosacea. There is a measurable effect on decreased self esteem and mood as reported by an NRS survey [202]. An association with depression has also been reported [8]. In a recent study of 308 subjects with mild to moderate rosacea, it was noted that rosacea had a moderate negative effect on quality of life. In this study, women were more affected than men [9]. Kini *et al.* found that rosacea's effect on quality of life was similar to that of leg ulcers, vitiligo and occupational contact dermatitis [10].

FUTURE SCIENCE part of fsg

Rosacea subtypes

Our understanding of the etiology of this disease remains elusive – possibly due to varying clinical findings. In an attempt to better classify phenotypes in rosacea, the NRS expert committee has defined four basic rosacea subtypes: erythematotelangiectatic, papulopustular, ocular, phymatous; and one variant, granulomatous rosacea [11].

Erythematotelangiectatic rosacea (ETR) is defined by the presence of one or more of the following: persistent central facial erythema, flushing (transient erythema), telangiectasia, dryness, topical sensitivity or facial edema (Figure 1) [11]. Based on these criteria, patients with solely telangiectasia may be given the diagnosis of ETR. As such, some argue that the ETR criteria is not stringent enough and may inadvertantly include erythematotelangiectatic photoaging, which also presents with facial telangiectasia [12]. The presence of symptomatic flushing and/or topical sensitivity can help discriminate ETR from photoaging, as photoaging is generally asymptomatic [13]. The typical flush of rosacea generally involves the central face and lasts longer than 10 min [14]. Flushing may be triggered by a variety of emotional stimuli such as anxiety and stress, as well as external stimuli such as heat, wind, spicy foods and alcohol. It is important to distinguish rosacea flushing from other more serious causes of flushing, such as carcinoid syndrome and pheochromocytoma. These entities are generally associated with other features such as gastrointestinal symptoms in carcinoid syndrome and hypertension in pheochromocytoma [15].

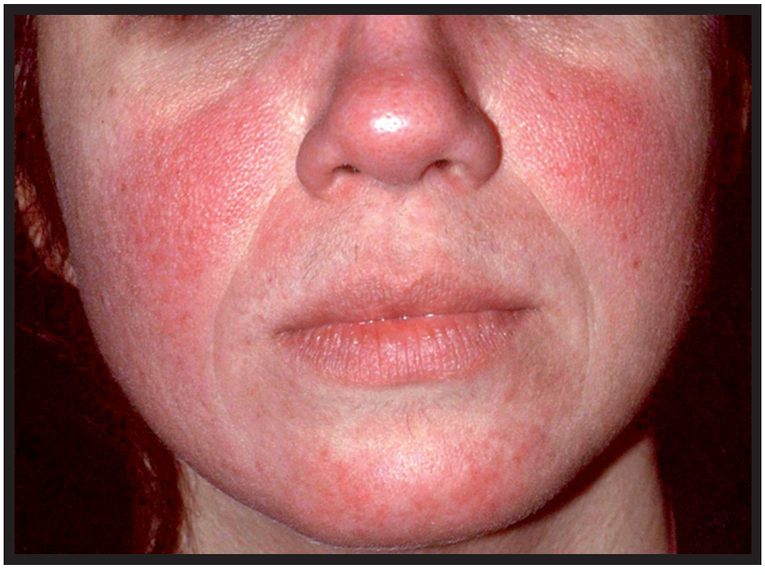

Figure 1. Erythematotelangiectatic rosacea: persistent centrofacial erythema and telangiectasia.
Reprinted with permission from © National Rosacea Society.

Papulopustular rosacea (PPR) is characterized by persistent central facial erythema accompanied by erythematous inflammatory papules and pustules that may mimic the inflammatory acne lesions (Figure 2). The lack of comedones in rosacea is a distinguishing feature from acne. As in ETR, these patients may have telangiectasia, edema and may endorse flushing symptoms and facial sensitivity [11].

Phymatous rosacea is the most disfiguring type of rosacea. This type is defined by areas of facial tissue hypertrophy with an irregular pitted texture due to prominently dilated follicles (Figure 3). The most commonly affected area is the nose, known as rhinophyma; however, other facial structures such as chin, ears, forhead, cheeks and eyelids can be affected [11]. Histologically, phymas demonstrate connective tissue hypertrophy, fibrosis and sebaceous hyperplasia [14,16]. Central facial erythema, inflammatory papules and telangiectasia may be present; however, these patients often do not have prominent flushing and facial sensitivity that may be more associated with other subtypes. Within the spectrum of phymatous rosacea, 'glandular rosacea' should be mentioned. Glandular rosacea is not a subtype defined by the NRS expert panel, but has been discussed as a separate variant by Crawford *et al.* [14]. These patients have greasy sebaceous skin, nontransient facial erythema and large inflammatory papules and nodulocystic lesions that are more reminiscent of acne than rosacea. This phenotype is important to discuss because of its potential to be confused with acne [14].

Ocular rosacea is a type of rosacea that can frequently be seen in association with other subtypes of rosacea; however, it can precede the cutaneous manifestations making the diagnosis difficult (Figure 2). These patients often complain of burning, itching stinging and dryness of the eye [11]. These symptoms are attributed to tear film abnormalities [17]. They may also endorse photophobia. Examination of the eyes may reveal blepharitis, conjuctivitis and lid telangiectasia. They may also complain of frequent chalazion. Uncommonly, ocular rosacea can result in severe ocular complications such as corneal damage, scleritis and iritis [7,11].

One rosacea variant, granulomatous rosacea, was defined by the NRS expert committee. It is defined by non-inflammatory, firm, uniform yellow-brown or red papules that may occur on otherwise normal skin. Other features such as flushing, telangiectasia, and facial erythema are not needed for diagnosis [11]. Some argue that this entity is not within the rosacea spectrum, and instead should be classified along with other granulomatous facial dermatoses including perioral dermatitis and lupus dissminatus facei [14].

Etiology

As we move into an age of targeted therapy, identifying factors involved in disease pathogenesis is crucial. Recent studies suggest that there are a few common features present in most patients with rosacea that have been appreciated clinically and histologically. These features are: angiogenesis, the presence of abundant blood vessels; lymphangiogenesis, the presence of increased lymphatics, which has been noted in not just phymatous rosacea but also in early stages of rosacea; and inflammation – as evidenced clinically by facial papules, pustules and erythema [18,19]. How these features arise, unfortunately thus far has remained unclear. Studies suggest that there may be a genetic predisoposition to the development of rosacea; however, specific genetic factors have not yet been clearly identified [20,21]. Fortunately, there has been resurgence in research on this disease, and some potential factors have been identified. Here some of the most prominent theories will be discussed.

Vascular hyperreactivity & neuropeptides

Many rosacea sufferers, especially those with ETR and PPR, have a predisposition to easy flushing caused by a variety of stimuli such as spicy foods, red wine, climactic extremes and stress. The flush is often associated with burning and tingling sensations. Furthermore, these frequent episodes of flushing worsen other symptoms, such as nontransient erythema and inflammatory papules. This suggests that hyperreactive vasculature and vasodilation are important in rosacea pathogenesis. The important role of abnormal vasculature is supported by studies demonstrating improvement in symptoms of rosacea-related flushing and facial sensitivity when vessel ablation is achieved by laser treatment [22,23]. It is theorized that, over time, repeated episodes of vasodilation may lead to loss of vascular tone and permanent dilatation of dermal blood vessels and lymphatics. The dilated vessels become leaky further allowing for escape of inflammatory mediators and fluid resulting in cutaneous inflammation and telangiectasia **(Figure 4)** [24,25]. The etiology of the abnormal vascular response is not understood.

The production of inflammatory neuropeptides may be one mechanism by which inflammation in rosacea is generated and maintained. Somatic nerves respond to physiological stimuli such as heat, cold and UV light by producing neuropeptides [26]. Some neuropeptides have been found in higher amounts in rosacea skin including substance P and vasoactive intestinal peptide [23,27]. Ablation of vessels with pulsed dye laser (PDL) resulted in a decrease in substance P immunoreactive nerve fibers, correlating with an improvement in rosacea related signs and symptoms [23]. Interestingly, substance P promotes vasodilation, increases vascular permeability and promotes recruitment and activation of inflammatory cells [28,29]. *In vitro* and *in vivo* mouse studies also suggest that substance P may promote angiogenesis [30].

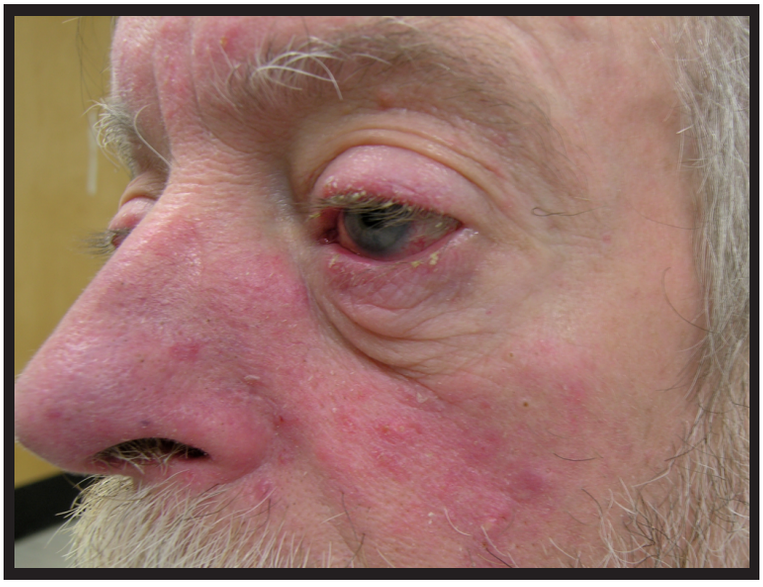

Figure 2. Papulopustular rosacea and ocular rosacea: presence of centrofacial erythema and inflammatory papules. This patient also has evidence of ocular rosacea (blepharitis and conjunctivitis).
Reprinted with permission from © National Rosacea Society.

UV light & extracellular matrix damage

One long considered theory is that UV light exposure contributes to rosacea. Rosacea occurs on the face, a chronically sun-exposed location, and studies have shown that photosensitive skin type is a risk factor for rosacea development [20,31]. Flushing may be provoked by acute sun exposure in some rosacea patients [31]. Acute

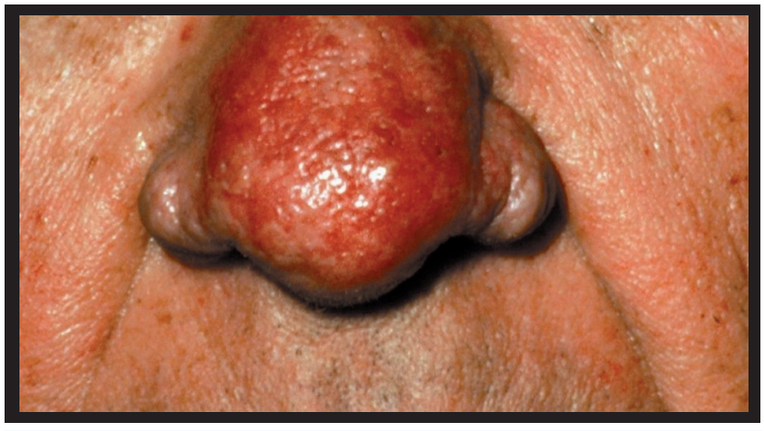

Figure 3. Phymatous rosacea. Skin thickening and enlargement of nose. Patient also has persistent erythema and telangiectasia.
Reprinted with permission from © National Rosacea Society.

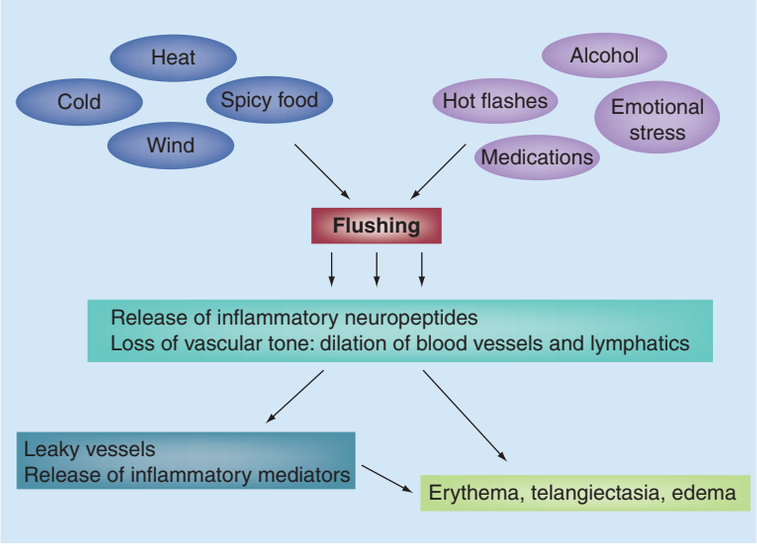

Figure 4. Vascular hyperreactivity theory. In this theory, various external and internal stimuli induce profound and recurrent flushing in the rosacea-affected individual. During the flush, proinflammatory neuropeptides and other inflammatory mediators are released. With time, repeated flushing produces dilation of blood vessels and lymphatics. These factors result in erythema, edema and telangiectasia.

UV exposures can produce cutaneous vasodilatation, erythema and elaboration of the angiogenic factors, VEGF, bFGF and IL-8 [32,33]. It has been speculated that new vessels that arise as a result are leaky, resulting in cutaneous inflammation via escape of inflammatory mediators [34]. UV light has been shown to stimulate production of substance P and calcitonin gene-related peptide from cutaneous nerves [35], providing a potential mechanism of producing inflammation.

Biopsies of rosacea affected skin often show evidence of solar elastosis, a papillary dermal amorphous material related to sun damage and a marker for dermal extracellular matrix damage [14,19,36]. UV radiation is a potent instigator of vascular and dermal matrix damage via generation of reactive oxygen species (ROS) and upregulation of matrix metalloproteinases (MMPs) [37]. In histologic evaluation of rosacea skin biopsies, Aroni *et al.* noted dilation of vessels in areas of solar elastosis [19]. This damaged connective tissue may be unable to maintain normal vessel structure and function, and thus may permit leakage and accumulation of inflammatory mediators and inflammatory cells. This may lead to the inflammation seen in the disease [14]. Moreover, recent studies by Varani *et al.* demonstrated that damaged collagen can promote angiogenesis [38]. It should be noted that factors other than UV light including inflammation-generated ROS may be important contributors to the extracellular matrix damage seen in rosacea.

Recent epidemiologic studies suggest that sun exposure may be more of a factor in the erythematotelangiectatic subtype rather than papulopustular subtype. Powell *et al.* published a study of Irish patients with PPR. No association with extent of sun exposure, nor clinical evidence of photodamage was found [39]. Furthermore a recent Korean study showed that higher levels of sun exposure correlated with the presence and severity of erythematotelangictatic rosacea, but not PPR [40]. This raises the question of whether or not these two types of rosacea are related, or if they are separate entities. Further studies are needed to better understand this issue. One recent study raised the possibility that UV may be pathogenic in the development of granulomatous rosacea. In this small retrospective study, lesions of granulomatous rosacea were associated with increased solar elastosis and higher levels of MMP-9 compared with nongranulomatous lesions. MMP-9 is induced by ROS and UV light to degrade type IV collagen resulting in matrix damage. This raises the possibility that UV may be pathogenic in the development of granulomatous rosacea [41].

Oxidative stress

Reactive oxygen species have been implicated in the pathogenesis of rosacea. Bakar *et al.* found that ROS (superoxide, hydroxyl, hydogen peroxide and hypochloride) levels in PPR skin was higher than in normal controls [42]. In the skin, high levels of ROS can be generated by exposure to UV light and external chemicals. They may also be produced by leukocytes participating in active cutaneous inflammation [43]. ROS induce signal transduction to activate proinflammatory responses, and pathways that induce the production of matrix degrading enzymes, MMPs [44,45]. These responses cause extracellular matrix damage, as well as potentially perpetuate cutaneous inflammation [43].

Humans, like other aerobic organisms, have developed endogenous antioxidant systems to protect from ROS induced damage [43]. Recently, a couple of small studies suggested the possibility that elevated ROS found in rosacea are due to an inherent defective antioxidant system in these patients. Oztas showed decreased cutaneous superoxide dismutase (SOD) activity in more severe forms of rosacea. With milder rosacea, SOD was increased, whereas it decreased with increased disease severity. The authors could not elucidate if the decreased SOD is the cause, or the result of rosacea inflammation [46]. Tisma *et al.* indicated lower levels of serum total antioxidative potential in rosacea patients [47]. Yacizi *et al.* investigated the association of rosacea with mutations in genes encoding the free-radical quenching proteins, glutathione-*S*-transferases. They specifically evaluated *GSTM1*, *GSTT1* and *GSTP1* genes encoding particular GST isoforms. In this study of 45 rosacea

subjects compared with 100 age, sex and ethnically matched normal controls, they found an association of null mutations in *GSTM1* and *GSTT1* with rosacea [21]. Larger studies are needed to investigate this correlation further.

Demodex

Demodex is a common commensal organism of human skin that is often found in the same skin regions that are affected by rosacea **(Figure 5)** [48]. For many years, there has been suspicion that it is a factor in rosacea pathogenesis and numerous studies have been undertaken to evaluate Demodex's role in rosacea. A recent retrospective meta-analysis of 48 English and Chinese language articles showed a significant association between Demodex infestation and the development of rosacea [48]. Antimiticidal therapies have been reported effective in the treatment of papulopusular rosacea, which also links Demodex to the disease pathogenesis [49,50]. However, the fact that some of our most effective treatments for rosacea are not known to be miticidal is a vexing issue in implicating Demodex as the sole cause of rosacea [51,52]. This is further complicated by the presence of studies demonstrating that clinical improvement of rosacea did not always correspond to a decrease in Demodex population [53,54]. It is possible that rosacea-affected skin provides a permissive environment for Demodex proliferation and that Demodex, in some cases, acts as a cofactor to promote further inflammation [55]. As Demodex mites exist in a symbiotic relationship with the host human skin, it is difficult to tell if our therapies are causing improvement by directly killing the mite or changing the host cutaneous milieu to one that is less inhabitable. From the aforementioned meta-analysis, it is unclear if Demodex is an etiologic factor in all subtypes of rosacea, as the subtypes were not separated in this study [48]. Further studies should be undertaken to evaluate Demodex prevalence in each subtype of rosacea.

Recently, in the *British Journal of Dermatology*, Lacey and colleagues suggested that Demodex mite itself is not the problem, but instead a bacteria harbored within the mite [56]. They isolated one such bacterium, *Bacillus oleronius*, from a Demodex mite. A peripheral blood mononuclear cell proliferation assay was performed and they found that patients with PPR were more immunoreactive to *B. oleronius* than those without. This suggests that the bacteria, rather than the mite, could be initiating an immune response creating the inflammatory papules and pustules seen in rosacea. *B. oleronius* is susceptible to tetracycline type antibiotics [56] and this theory could explain the effectiveness of tetracyclines in the treatment of rosacea. A subsequent study of 59 patients with various ocular surface diseases noted a significant association between serum immunoreactivity to *B. oleronius* and facial rosacea, inflammation of eyelid margin and ocular Demodex infestation [57]. That having been said, not all subjects with facial rosacea and lid margin inflammation had positive immunoreactivity to *B. oleronius*. At this point, it is probably reasonable to conclude that Demodex and *B. oleronius* act as pathogenic cofactors in some cases of rosacea. Arguably the effectiveness of submicrobial dose doxycycline and other non-antimicrobial therapies in rosacea treatment points to rosacea not being solely an infectious disease. Further studies are needed.

Figure 5. Light microscopy of Demodex mites obtained from surface skin scraping.

Dysregulation of innate immunity

The innate immune system is an antigen independent defense system that provides an immediate response to pathogens. Multiple external stimuli such as UV light and chemical insults can also trigger the innate immune system. This occurs via receptors in the pattern recognition system which includes Toll-like receptors (TLRs) and nucleoside-binding domain and leucine-rich repeat containing receptors [58]. When the innate immune system is triggered there is an increase in inflammatory cytokine expression and production of antimicrobial peptides. These antimicrobial peptides help kill off microbes, and are also proinflammatory themselves. External agents thought to be triggers or factors in rosacea pathogenesis such as UV light, climactic changes and microbes can trigger the innate immune system and result in inflammation [59].

Yamasaki *et al.* demonstrated that dysregulation of the innate immune system is likely a central pathogenic step in rosacea development **(Figure 6)** [60]. In this elegant study, they found that the proinflammatory and angiogenic form of the antimicrobial peptide cathelicidin, LL-37, was overexpressed in rosacea skin. When LL-37 is injected into mouse skin, cutaneous inflammation

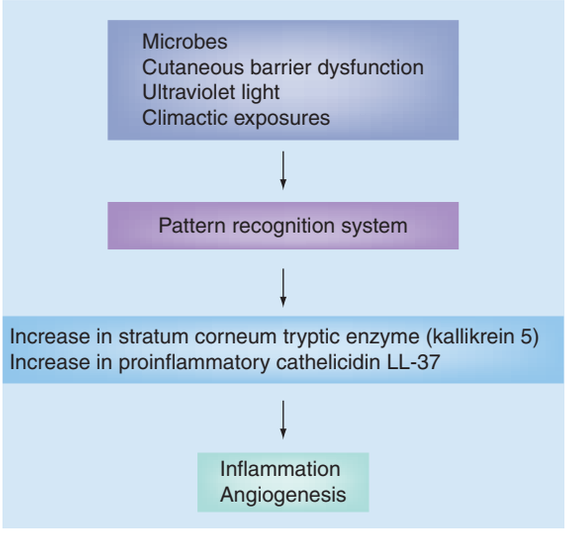

Figure 6. Various external stimuli trigger the innate immune system via the pattern-recognition system, which includes Toll-like receptors. Toll-like receptor 2 appears responsible for an elevation in stratum corneum tryptic enzyme (kallikrein 5) which produces an increase in the proinflammatory form of the antimicrobial peptide cathelicidin [59,60].

occurs that is similar to that seen in rosacea. The LL-37 form of cathelicidin begins as an inactive propeptide. When the innate immune system is triggered, the pro-peptide is cleaved by proteases to the active LL-37. The authors demonstrated an overexpression of a serine protease known as stratum corneum tryptic enzyme, kallikrein 5 (KLK5). This protease is responsible for producing the LL-37 form of cathelicidin [60]. Yamasaki *et al.* has more recently found that TLR2 is more highly expressed in rosacea skin than normal controls. Moreover, overexpression of TLR2 resulted in an increased expression of KLK5 in normal human epidermal keratinocytes *in vitro*. Thus, it appears that the elevated levels of KLK5 in rosacea skin can be attributed to increased TLR2. The authors concluded that upregulation of TLR2 could explain the increased reactivity of rosacea skin to environmental stimuli [59].

Mast cells

Aroni *et al.* recently observed increased numbers of mast cells in biopsies of rosacea-affected skin. Mast cells are known to produce inflammation, angiogenesis, extracellular matrix destruction and tissue fibrosis [19,61,62]. These are all features that have been described in rosacea. In this study, the authors did not find an association between mast-cell concentration and density of blood vessels; however, instead, found an association with disease duration. The authors hypothesized that mast cells may be responsible for sustaining blood vessels in rosacea [19]. Aloi *et al.* also observed an increased number of mast cells in phymatous rosacea [16]. As mast cells have been implicated in fibrotic disease, it is possible that the collagen fibrosis demonstrated histologically in phymatous tissue may be a result of mast cell activity [16,61].

Treatment

Although the pathogenic steps resulting in rosacea clinical features are not all known, our evolving understanding of the disease process has allowed us to consider new methods for treatment, and has helped us understand the potential mechanisms of our current therapies. Current principles in rosacea treatment include minimizing triggers of cutaneous irritation and flushing and therapies to decrease angiogenesis and inflammation. Treatment options and strategies will be reviewed; however, it must be noted that many of the studies evaluating rosacea treatment are small and of poorer quality [63].

Standard & first line therapies

Prevention

For all types of rosacea, flushing trigger avoidance and maintenance of skin barrier is important. Common triggers include sunlight, heat, wind, stress, spicy foods, alcohol and exercise [9,14]. As mentioned before, flushing may provoke rosacea by the release of proinflammatory neuropeptides and cytokines. Also, one could speculate that the flushing response may change the cutaneous environment, that is, temperature or pH. This change in the environment may increase activity of proteases that are involved in cleaving procathelicidin into the proinflammatory LL-37 [60]. Many physicians routinely recommend sunscreens, as UV light has been shown in some cases to be a flushing trigger. Furthermore, as mentioned previously, chronic UV exposure may be pathogenic – particularly in ETR patients, by inducing inflammation and damaging the extracellular matrix.

Emollients are often helpful adjuncts in the treatment of rosacea, as they can minimize symptoms of burning, stinging, itching, topical sensitivity and dryness [64,65]. This may result from the repair of disrupted stratum corneum and barrier function that has been reported in rosacea patients [66]. The etiology of the barrier dysfunction is not known; however, it may be a product of inflammation [66]. Proinflammatory cathelicidin and other antimicrobial peptides are upregulated in skin injury [67] and one can speculate that improving barrier function in rosacea may decrease their expression. Other measures to protect the skin barrier include avoidance of excessively alkaline and abrasive cleansers, alcohol-based topical agents, fragrances and other known irritants [68].

Topical antimicrobials

Some of the most commonly prescribed medications for rosacea include topical antimicrobial agents. As discussed earlier, *B. oleronius* may play a role in rosacea pathogenesis; however, a definitive bacterial agent has not been identified as the primary etiologic agent. Despite this, antimicrobials have excellent efficacy possibly due to their anti-inflammatory properties. Topical metronidazole is efficacious against the inflammatory papules and pustules of rosacea, and has moderate effects on erythema [69,70]. Its mechanism of action has been attributed to activity against ROS [71,72]. Topical metronidazole is produced commercially in different concentrations (0.75 and 1%) and in different vehicles (e.g., gel, cream and lotion). A meta-analysis by Yoo *et al.* suggested that different concentrations, different vehicle and dosing (once versus twice daily) all had equivalent efficacy [73].

Sodium sulfacetamide-sulfur also decreases papules and pustules with moderate effect on erythema. The mechanism of action of sodium sulfacetamide-sulfur in rosacea is unknown, but one activity may be an anti-Demodex effect [74]. There are multiple preparations available including cleansers, creams, foams and preparations with added sunscreens [75]. Several studies suggest that sodium sulfacetamide 10% and sulfur 5% lotion produce improvement in inflammatory lesions [76,77]. Small comparative studies suggest that it is non-inferior to metronidazole in treating papules and pustules, and may be more effective in treating the erythema [78,79]. That said, larger studies are needed to identify true comparative efficacy. This author finds sodium sulfacetamide-sulfur ophthalmic preparations to be helpful in the treatment of blepharitis associated with ocular rosacea.

Other antimicrobials such as topical clindamycin, erythromycin and benzoyl peroxide have been noted to be useful as second-line agents [80–82]. Recently, benzoyl peroxide-clindamycin and benzoyl peroxide-erythromycin combination products initially designed for treatment of acne have been reported as effective in treating the papules and pustules of rosacea [83,84]. However, caution must be used in those patients with a tendency towards facial dryness and dermatitis as these products may have a greater tendency to irritate. Ozturkcan *et al.* performed a small study comparing benzoyl peroxide-erythromycin gel with topical metronidazole. They found that both treatments effectively decreased inflammatory papules in rosacea. Topical metronidazole, however, appeared more effective [54].

Topical azelaic acid

Similar to topical antimicrobials, topical azelaic acid is helpful in treating the papules and pustules of PPR. Erythema is also reported to be decreased to some extent [85–87]. Efficacy studies show that it is as good as, and possibly more efficacious, than topical metronidazole for the treatment of papules and pustules of rosacea [88]. The mechanism of action may be related to decreasing ROS [89]. Azelaic acid is a good choice for pregnant patients with rosacea as it is pregnancy category B [90]. One drawback of this medication is the potential for short-lived burning and stinging sensations upon application, especially in those with significant facial sensitivity. Overall, however, azelaic acid is well tolerated [86].

Oral antibiotics

Tetracycline antibiotics have long been a cornerstone of rosacea therapy. Commonly used drugs in this class are tetracycline, minocycline and doxycycline. There are various dosing strategies for these medications. Classically, these have been used at antimicrobial doses: doxycycline and minocycline 50–200 mg/day, tetracycline 250–1000 mg/day [91]. These are often used for flares for several weeks and then tapered completely off or to the lowest dose necessary to maintain remission. Often, they are accompanied by use of topical therapies that are eventually used as maintenance therapies. Interestingly, there are very few studies evaluating the efficacy of these medications at antimicrobial doses [63] despite being frequently used by dermatologists as first-line agents for more moderate to severe cases of rosacea. Tetracycline antibiotics appear to have greatest effect against papules and pustules, although there can be some improvement in erythema and symptoms such as facial sensitivity/stinging [63,92]. They are also important in decreasing the inflammation and manifestations of ocular rosacea and decreasing papules in granulomatous rosacea [63,93]. Some side effects of this class of medications include photosensitivity, gastrointestinal upset, hyperpigmentation, pseudotumor cerebri, hepatotoxicity, as well as the potential for inducing bacterial resistance with long term use [94].

Tetracyclines have multiple possible mechanisms of action in rosacea. Bacteria such *B. oleronius* are sensitive to tetracycline-type antibiotics [56]. Many experts believe, however, that the efficacy is related to anti-inflammatory properties rather than antimicrobial properties. Some studies suggest that tetracycline-type antibiotics can decrease levels of proinflammatory cytokines, TNF-α, IL-1B, IL-8 and IL-10 [95,96]. Tetracyclines also appear to inhibit the extracellular matrix degrading activities of MMPs [95] and may even decrease their expression [97]. This helps to protect and maintain the integrity and function of the extracellular matrix and vessel basement membranes. Furthermore, tetracyclines in *in vitro* studies reduce ROS, by unclear mechanisms [95]. Lastly, it has been hypothesized that,

tetracycline-type antibiotics may exert effect on the innate immune system, by acting as indirect serine protease inhibitors – potentially suppressing the generation of proinflammatory cathelicidin LL-37 [60].

One of the criticisms of the antimicrobial dosing regimens is their potential to promote development of resistant strains of bacteria. Thus investigations were taken to evaluate anti-inflammatory but not antimicrobial dosing, and now anti-inflammatory (aka sub-antimicrobial) dose doxycycline is one of our new agents in our armamentarium. At these doses there is no antimicrobial activity, but there are anti-inflammatory effects. In the clinic, this is often administered as doxycycline hyclate 20 mg orally twice daily [98] or a proprietary formulation of 40 mg (30 mg immediate plus 10 mg delayed release doxycycline) [99]. In two randomized controlled 16-week trials, Del Rosso *et al.* compared the efficacy of the proprietary formulation of anti-inflammatory dose doxycycline with placebo and found a statistically significant improvement in inflammatory papules in the anti-inflammatory dose doxycycline group. However, only 22% of patients reported near or complete clearing of these inflammatory lesions. There was no improvement in erythema in this study [99]. In a follow up study, Del Rosso *et al.* found that anti-inflammatory doxycycline combined with metronidazole 1% once daily was equally effective in improving inflammatory papules and erythema as doxycycline 100 mg/day when combined with metronidazole 1% once daily [100]. A study comparing anti-inflammatory doxycycline with antimicrobial dose doxycycline in the absence of any other therapy would be helpful in defining equivalence of these therapies. Anti-inflammatory doxycycline appears to be a promising therapy especially when used in combination with topical treatment, such as azelaic acid or topical metronidazole [101]. Longer term studies are needed to assess if remission is maintained with long term use, as well as to better delineate the side effect profile of long term use.

■ Other systemic antibiotics

Macrolides such as azithromycin, clarithromycin and erythromycin have been shown in small studies to improve inflammatory lesions, erythema and ocular symptoms in rosacea [102–105]. Their proposed mechanism of action is decreasing oxidative stress [42] possibly by blocking neutrophil generation of free radicals [106,107] and boosting SOD activity [42]. Furthermore they appear to decrease production of proinflammatory cytokines [42]. Ideal dosing regimens are unknown, but doses used in recent studies are at antimicrobial levels and as such have the potential to produce bacterial resistance.

Oral metronidazole, 200 mg twice daily, is often used for treatment of rosacea in Europe. In a small (40 subjects) 12-week double-blind study, this drug was shown to be equivalent to oxytetracycline 250 mg twice daily in the treatment of PPR [108]. Askoy *et al* found that oral metronidazole 250 mg twice daily was inferior to oral tetracycline 500 mg twice daily [9], unfortunately this study was quite small and only included four subjects treated with oral metronidazole. Side-effects include headache, nausea, loss of appetite, a metallic taste and rare occurrence of neuropathy and seizures. Alcohol abstinence is required during use [90].

Second-line & nonstandard medical therapies

■ Topical retinoids

Topical retinoids are currently approved by the US FDA and various European national health authorities for the treatment of acne and photoaging. Part of their efficacy in these conditions can be attributed to their ability to repair damaged extracellular matrix and to decrease inflammation [109]. These same properties may be helpful in the treatment of rosacea. As discussed previously, damage to the extracellular matrix due to UV light, ROS and inflammation may play a role in rosacea development. Thus it is reasonable to conclude that matrix repair may lead to improved vessel support, decreased inflammation and angiogenesis, resulting in improvement and prevention of rosacea symptoms. Moreover, in an *in vitro* study, Liu *et al.* demonstrated that TLR2 is downregulated by all-trans retinoic acid in human monocytes [110]. Since TLR 2 is elevated in rosacea skin[59], it is theoretically possible that all-trans retinoic acid could downregulate TLR2 in rosacea. Further studies are needed to evaluate this possibility. Lastly, retinoids have been shown *in vitro* and *in vivo* to decrease UV-induced VEGF production and angiogenesis [33].

Very few studies exist that investigate the action and efficacy of topical retinoids in rosacea. In a couple of small studies, the topical retinoids tretinoin and adapalene decreased inflammatory papules and pustules in rosacea [111,112]. Vienne *et al.* found retinaldehyde 0.05% cream used for 5 months produced a reduction in the erythema in patients with ETR [113]. Some have been hesitant to recommend retinoids in rosacea, as they can be irritating – causing erythema and scaling. Thus, it may be prudent to avoid their use in patients with severe facial sensitivity, erythema and dermatitis. At this point, retinoids remain a second-line agent, but further studies on their use in rosacea treatment are warranted. In the treatment of photoaging, the dermal reparative effects of retinoids may take several months to result in clinical improvement [114]. Therefore, if further clinical studies are undertaken to evaluate topical retinoid effects in rosacea, it would be ideal to treat for 6 months or longer.

Isotretinoin

Isotretinoin is an infrequently employed but effective medication for rosacea. Isotretinoin is often used in acne at doses of 0.5–1 mg/kg, with the goal of reaching 120–150 mg/kg cumulative dose [115]. It is thought to decrease sebaceous glands size and activity, and decrease inflammation [116]. Several small studies have demonstrated effectiveness in rosacea [117,118]. Isotretinoin has been shown to improve inflammatory lesions, erythema, edema and nasal volume in some studies [119]. In rosacea, the optimum dose and duration of isotretinoin treatment has not yet been defined. Furthermore, as rosacea is a chronic and relapsing condition, isotretinoin treatment is likely remittive, but not curative. Earlier studies employed doses of 0.5–1.0 mg/kg [117–119]. More recently, some have advocated for lower dose isotretinoin therapy. Gollnick *et al.* recently reported in a randomized controlled trial that isotretinoin 0.3 mg/kg was more effective than doses of 0.5 and 0.1 mg/kg. This dose of 0.3 mg/kg was more effective in clearing papules and pustules during the 12-week treatment period than doxycycline 100 mg day. There was also a somewhat greater improvement in rhinophyma in the isotretinoin group. In this study, the doxycycline-treated group had a slightly greater improvement in clearing erythema and edema [120]. Erdogan *et al.* evaluated 22 patients on isotretinoin 10 mg/day for 16 weeks. Subjects had a statistically significant improvement in erythema, telangiectasia and inflammatory papules and pustules. There also seemed to be an improvement in ocular manifestations of rosacea. They did not evaluate time to relapse [121].

Miticidal treatment

As Demodex has been implicated in the pathogenesis of rosacea, miticidal agents have been investigated. In a small study, Kocak M *et al.* treated PPR subjects with permethrin 5% twice daily for 2 months and found improvement in inflammatory papules compared with placebo [49]. Mostafa *et al.* demonstsrated that permethrin 5% was effective in the treatment of PPR and had a treatment response similar to metronidazole 0.75% [122]. Other miticidal agents have not been investigated in clinical trials; however, ivermectin in one case report has been helpful for recalcitrant rosacea in conjunction with permethrin [50].

Medical approach to flushing (flushing antagonists)

Rosacea flushing can occur in response to a variety of environmental stimuli, such as heat and cold, spicy foods and hot beverages, as well as emotional stimuli. In some cases, these triggers can be avoided and flushing minimized. However, for some rosacea sufferers, certain triggers (e.g., stress and exercise) cannot be avoided. Sadly, flushing remains one of the more difficult symptoms to treat. Oral clonidine and oral propranolol have been suggested to be helpful in few small studies [123,124]. Clonidine 0.05 mg twice daily in one small study decreased the malar temperature [125], but did not prevent flushing in response to known triggers. Craige *et al.*, suggested that subjects with anxiety/emotion provoked flushing benefit the most from β-blocker therapy [124]. Conversely nadolol, another β-blocker, was found not to show a statistically significant decrease in flushing reactions for 15 subjects with ETR. That said, there was a trend towards improvement, and it is possible that with a greater sample size, this may have reached significance [126]. Selective serotonin or serotonin-norepinephrine reuptake inhibitors have been shown to be helpful in perimenopausal flushing [127]. It is unclear if these would be helpful in attenuating rosacea-induced flushing. Further research into this issue may be of benefit. Overall, there is a paucity of data to support routine use of all the aforementioned medications; however, they may be worthwhile to try in those patients with recalcitrant or debilitating flushing.

Topical vasoconstrictors

Recently, there has been interest in using topical vasoconstrictors to treat rosacea. A variety of α-adrenoceptor agonists, such as phenylephrine and oxymetazoline are used in over the counter nasal sprays designed to decrease nasal congestion. These agents decrease the visibility of vessels by producing vasoconstriction, and may also have antioxidant and anti-inflammatory properties [128,129]. Shanler *et al.* reported significant improvement in redness and flushing in several ETR patients treated with topical oxymetazoline [130,131]. Major concerns in the use of these agents for nasal congestion include tachyphylaxis and rebound vasodilatation. The patients treated by Shanler *et al.* did not experience these side effects even with prolonged (8–17 month) use. [130]. Due to the vasoconstrictive and anti-inflammatory effects, oxymetazoline is a compelling potential treatment that deserves further clinical study. Furthermore, other α-adrenergic receptor agonists, such as brimonidine may prove useful.

Nonmedical therapies

Laser- & light-based therapies

Lasers that target blood vessels have been used to treat rosacea. In several studies, the PDLs at 585 and 595 nm have been shown to effectively reduce rosacea-related erythema and telangiectasia [22,132,133]. Furthermore, small studies suggest that these lasers may actually improve facial sensitivity and flushing to some degree [22,23,134]. Treatment with these lasers have been found to improve quality of life [22]. Early lasers and treatment settings often produced purpura that could last up to

a few weeks. More and more, lasers with nonpurpurogenic settings and cooling devices to limit purpura and other collateral epidermal damage are being used [135]. Less purpurogenic settings may be less effective and a greater number of treatments may be required [135]. The duration of rosacea erythema and telangiectasia clearance and improvement is not known; however, given the chronicity of the disease, most patients require periodic maintenance treatment [135].

Unlike lasers that produces one wavelength, intense pulse light (IPL) devices emit noncoherent light at multiple wavelengths. Filters are used to select for desired wavelengths. Several studies have demonstrated that IPL can reduce erythema and telangiectasia in rosacea [136–139]. Neuhaus *et al.* performed a split faced study in 29 patients with ETR. A total of 22 of these patients were treated with IPL on one side and PDL (595 nm) on the other side. Four patients had IPL to one side and no treatment to the other side and the last four patients had PDL to one side and no treatment to the other side. A series of three treatments were performed at 4-week intervals, with the final evaluation occurring 4 weeks after the last treatment. The researchers found that IPL and PDL both improved erythema, telangiectasia and symptoms including flushing, dryness, burning and pruritus. IPL and PDL appeared equivalent in producing this improvement [134].

Carbon dioxide laser has been used to treat rhinophyma by ablating the excess phymatous tissue. In a recent study by Madan *et al.*, carbon dioxide laser was shown to be well tolerated and effective in treating phyma [140]. The side effects were few and included hypopigmentation, scarring, open pores and pain associated with anesthetic injection. It should be noted that the majority of subjects in this study were Caucasian. Caution should be taken in patients with darker skin tones as they have a higher risk of pigmentary disturbances after ablative therapy. Other lasers used to ablate rhinophyma include the 1470 nm diode laser [141,142] and argon laser [143].

■ Surgical therapies

For those patients with disfiguring rhinophyma, several surgical approaches may be used to debulk excess tissue. These include scalpel excision, electrosurgery, electrocautery, dermabrasion, cryosurgery and cryotherapy [144,145]. Specifics of these procedures are beyond the scope of this article; however, they all have risk of scarring and pigmentary disturbances.

Rosacea subtype-based treatment selection

Rosacea is a chronic relapsing condition, and treatment is focused on controlling symptoms of the disease. All patients should be educated on appropriate gentle basic skin care and sunscreen use as outlined previously. Avoidance of flushing and blushing triggers is also key. Identifying the subtype of rosacea may assist in designing appropriate treatment regimens. Briefly, these options are outlined (Table 1).

■ Erythematotelangiectatic rosacea

For the treatment of persistent erythema and telangiectasia seen in ETR, PDL and IPL are often quite effective [135]. Unfortunately, these therapies are often not covered by insurance and can be expensive. There are very few studies evaluating drug treatment of ETR. Based on studies primarily of PPR patients, persistent erythema in rosacea may be improved mildly to moderately by topical agents such as metronidazole, sodium sulfacetamide-sulfur and azelaic acid [76,78,86,146] and oral antibiotics [90]. Topical oxymetazoline and other topical α-agonists may also prove to be important in the treatment of ETR; however, further larger trials for safety and efficacy are needed prior to recommending their routine use. Treatments that improve persistent erythema may also be helpful in decreasing facial sensitivity [23].

Episodic flushing (transient erythema) is a very difficult symptom to manage. Avoidance of flushing triggers is an important preventive step. There is no drug that uniformly decreases flushing. However, those with severe and debilitating flushing may benefit from a trial of low dose β-blocker or low dose clonidine. Furthermore topical α-adrenergic agonists, such as oxymetazoline, show promise in preventing flushing and erythema; however, again routine use is best avoided until larger studies verify their safety and efficacy.

■ Papulopustular rosacea

Multiple topical and systemic therapies are available and effective in the treatment of PPR. For mild cases, monotherapy with topical metronidazole, topical azelaic acid, topical sodium sulfacetamide-sulfur or anti-inflammatory dose doxycycline are first-line therapies. Other topical antimicrobials such as topical benzoyl peroxide-erythromycin and benzoyl peroxide-clindamycin, as well as topical permethrin and topical retinoids can be used for patients who fail to respond or who are intolerant to the first-line agents. For more moderate to severe inflammatory lesions, topical agents may be combined with anti-inflammatory dose doxycycline or a short course of antimicrobial dose tetracycline type antibiotic or macrolide. If antimicrobial dose antibiotics are used, it is best to limit exposure to the shortest duration possible and to maintain remission with topical agents, such as azelaic acid and topical metronidazole [69,91,147]. If these more severe cases fail to improve with oral antibiotics, or antibiotics are not

tolerated or contraindicated, isotretinoin may be an effective second-line option. Transient erythema, nontransient erythema and telangiectasia associated with PPR are treated as described above in the discussion of ETR treatment.

Phymatous rosacea

Medical therapy of phymatous rosacea is challenging. Isotretinoin in small studies has been shown to decrease tissue hypertrophy and sebaceous hyperplasia [119]; however, the ideal duration of therapy and dose is not known. For most bothersome phymas, surgical or laser ablation is often needed. Inflammatory lesions seen in patients with phymatous rosacea are treated similar to that described for PPR; however, these patients tend to have less facial sensitivity and, as such, may be able to tolerate potentially more irritating therapies such as topical retinoids and benzoyl-peroxide products.

Ocular rosacea

The first step in treating ocular rosacea is identifying it. It is important for physicians to ask about ocular rosacea symptoms in patients with cutaneous evidence of rosacea [7,148]. Additionally, if ocular rosacea is suspected, it may be worthwhile to enlist the help of ophthalmologist to look for more sinister complications of ocular rosacea, especially if there are significant symptoms or inflammation. Lid hygiene is often an important basic step in managing ocular rosacea. This prevents crust build up and helps open plugged meibomian glands. Artificial tears are helpful in managing dry eye symptoms [148]. Topical antibiotics such as sodium sulfacetamide ophthalmic ointment, erythromycin ointment and metronidazole can be applied to the eyelids to manage milder forms of blepharitis [149]. For more advanced disease, systemic antibiotics, such as doxycycline are often required [148]. Recently, topical cyclosporine 0.05% emulsion in a small study has been demonstrated to improve rosacea-related eyelid abnormalities, meibomean gland inspissations and corneal changes (as measured by corneal staining). The authors concluded that these changes were due to anti-inflammatory properties and due to increased tear production [17]. Larger trials are needed to assess true efficacy in this disease.

Granulomatous rosacea

Granulomatous rosacea generally requires treatment with oral antibiotics; however, milder cases may respond to topical metronidazole. Isotretinoin has also been described to be effective in the treatment of this subtype [93]. Oral dapsone has been reported in two patients to improve granulomatous rosacea [150] and a couple of cases suggested that the topical calcineurin inhibitor pimecrolimus may be helpful in the treatment of granulomatous rosacea [151,152].

Table 1. Treatment options based on rosacea subtype.

Rosacea subtype	Treatment options
Erythematotelangiectatic	
Mild	Sun protection Trigger avoidance Emollients
Moderate–severe	Sun protection Trigger avoidance Emollients Laser- and light-based therapies
Second-line and nonstandard treatment	Propranolol or clonidine for severe flushing Topical vasoconstrictor (e.g., oxymetazoline) Topical azelaic acid Topical and oral antibiotics/antimicrobials Topical retinoids
Papulopustular	
Mild	Sun protection Trigger avoidance Emollients Topical azelaic acid Topical metronidazole Topical sodium sulfacetamide-sulfur Anti-inflammatory dose doxycycline Laser- and light-based therapies for persistent erythema
Moderate	Treatments as listed for mild papulopustular Consider combination anti-inflammatory dose doxycycline and topical agent Oral antimicrobial dose tetracycline, macrolide, metronidazole alone or in combination with topical agent
Severe	Treatments as listed for moderate papulopustular Isotretinoin for recalcitrant cases
Second-line and nonstandard treatments	Permethrin cream Topical benzoyl peroxide antibiotic combination products Topical clindamycin, erythromycin Topical retinoids
Phymatous	
	Surgical or laser ablation of excess tissue Isotretinoin Papulopustular component treated as described for papulopustular Sun protection and trigger avoidance
Ocular	
	Lid hygiene Artificial tears Topical antibiotics Systemic tetracyclines, macrolides Topical cyclosporine

Future perspective

Rosacea is a complex disease of varying clinical features that may have a negative impact on patients' lives [9]. The pathogenesis of rosacea has, thus far, been difficult to elucidate, not only due to its clinically pleomorphic features, but also because its genesis is likely multifactorial. Initial steps by the NRS expert committee to delineate standard subtypes will help with future research [11]. It allows us to explore the possibility that the different manifestations of rosacea may not be the result of the same pathologic processes. In the next few years, it is likely that further epidemiologic, genetic, histologic and biochemical studies will be undertaken to identify factors and features that are disparate or common between these subtypes. Furthermore, most treatment studies, thus far, have focused on the papulopustular subtype. New efforts are needed to identify easy and inexpensive treatments for the other subtypes. Having stated the need for future research, we cannot deny that there has been evolution in our understanding of the disease over the last few years. The recent identification of overexpression of cathelicidin and KLK5 in rosacea, allows us to consider designing therapies such as targeted KLK5 inhibitors for the treatment of rosacea [60]. It is likely that these and other serine protease inhibitors will be evaluated for rosacea treatment in the coming years. Acknowledging that studies implicate angiogenesis and abnormal neurovascular response in the pathogenesis of rosacea, raises the possibility of further investigation of topical vasoconstricting drugs [130], as well as drugs such as VEGF inhibitors that would prevent angiogenesis. Other potential treatments that may be worthwhile to investigate include use of antioxidants, mast cell inhibitors and agents to repair extracellular matrix damage. There is much more to learn about the cause and treatment of this common yet elusive disease, hopefully with recent renewed interest, we will be able to unlock its secrets in the coming years.

Financial & competing interests disclosure

The University of Michigan Dermatology Department has received grant funding from Coria/Valeant Pharmaceuticals for a rosacea treatment study. Lisa E Maier, acts as principal investigator on this trial, but does not receive any financial compensation. The author has no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed. No writing assistance was utilized in the production of this manuscript.

Executive summary

- Rosacea is a common, chronic inflammatory skin disorder with clinically heterogeneous features.
- The four subtypes of rosacea as defined by the National Rosacea Society expert committee are erythematotelangiectatic rosacea, papulopustular rosacea, phymatous rosacea and ocular rosacea.
- The underlying pathophysiology of the disease is not completely understood; however, it may be related to vascular hyperreactivity, neuropeptides, increased oxidative stress, UV light exposure, extracellular matrix damage, dysregulation of the innate immune system, Demodex mites or Demodex-related bacteria. There also appears to be a familial predisposition to its development.
- Treatment of rosacea focuses on alleviating signs and symptoms, as no cure has yet been found for the disease. Many studies evaluating the efficacy of various rosacea treatments are small and/or are of low quality.
- Basic care of rosacea skin includes sun protection, emollients and avoidance of flushing triggers.
- First-line treatments for papulopustular rosacea are topical metronidazole, topical azelaic acid, topical sodium sulfacetamide-sulfur and anti-inflammatory dose doxycycline. Antimicrobial dose tetracycline class antibiotics, systemic metronidazole and macrolide antibiotics may be needed for more advanced cases of papulopustular rosacea. These therapies target the inflammation seen in the disease, particularly the papules and pustules.
- Tetracycline class antibiotics used at antimicrobial doses have long been used by dermatologists to treat inflammatory lesions in rosacea. One of the criticisms of the antimicrobial dosing regimens is their potential to promote development of resistant strains of bacteria. Recent studies of anti-inflammatory dose doxycycline have demonstrated its effectiveness in decreasing papules and pustules. More comparative studies are needed to assess its efficacy compared with antimicrobial dose doxycycline and other tetracyclines.
- Isotretinoin is used as a second-line agent to treat papulopustular rosacea and early rhinophyma. The appropriate dose and duration of therapy has not yet been clearly defined.
- Topical oxymetazoline and other topical α-adrenergic receptor agonists are potentially promising future medical therapies to manage persistent rosacea-related erythema. Further studies are needed to assess efficacy and safety of these mediations.
- Pulsed dye laser and intense pulsed light are effective in decreasing rosacea-related persistent erythema and telangiectasia. In a couple of small studies, these therapies have also improved troublesome rosacea symptoms such as stinging, burning and flushing.
- Treatment of disfiguring phymatous rosacea often involves laser or surgical ablation of phymatous tissue.
- Future rosacea research should focus on understanding epidemiologic, genetic, histologic and biochemical factors and features that are disparate or common between the different subtypes of rosacea. Furthermore, researchers engaging in treatment-related research should try for larger sample sizes and separation of subtypes if at all possible.

Bibliography

Papers of special note have been highlighted as:

- ■ of interest
- ■■ of considerable interes

1 Schaefer I, Rustenbach SJ, Zimmer L, Augustin M. Prevalence of skin diseases in a cohort of 48,665 employees in Germany. *Dermatology* 217(2), 169–172 (2008).

2 Berg M, Liden S. An epidemiological study of rosacea. *Acta Derm. Venereol.* 69(5), 419–423 (1989).

3 Abram K, Silm H, Oona M. Prevalence of rosacea in an Estonian working population using a standard classification. *Acta Derm. Venereol.* 90(3), 269–273 (2010).

4 Alexis AF. Rosacea in patients with skin of color: uncommon but not rare. *Cutis.* 86(2), 60–62 (2010).

5 Khaled A, Hammami H, Zeglaoui F *et al.* Rosacea: 244 Tunisian cases. *Tunis. Med.* 88(8), 597–601 (2010).

6 Kyriakis KP, Palamaras I, Terzoudi S *et al.* Epidemiologic aspects of rosacea. *J Am Acad Dermatol.* 53(5), 918–919 (2005).

7 Chamaillard M, Mortemousque B, Boralevi F *et al.* Cutaneous and ocular signs of childhood rosacea. *Arch. Dermatol.* 144(2), 167–171 (2008).

8 Gupta MA, Gupta AK, Chen SJ, Johnson AM. Comorbidity of rosacea and depression: an analysis of the National Ambulatory Medical Care survey and National Hospital Ambulatory care survey – outpatient department data collected by the U.S. National Center for Health Statistics from 1995 to 2002. *Br. J. Dermatol.* 153(6), 1176–1181 (2005).

9 Aksoy B, Altaykan-Hapa A, Egemen D, Karagoz F, Atakan N. The impact of rosacea on quality of life: effects of demographic and clinical characteristics and various treatment modalities. *Br. J. Dermatol.* 163(4), 719–725 (2010).

10 Kini SP, Nicholson K, DeLong LK *et al.* A pilot study in discrepancies in quality of life among three cutaneous types of rosacea. *J. Am. Acad. Dermatol.* 62(6), 1069–1071 (2010).

11 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.* 46(4), 584–587 (2002).

■■ **Article defines the clinical rosacea subtypes.**

12 Danby FW. Rosacea, acne rosacea, and actinic telangiectasia. *J. Am. Acad. Dermatol.* 52(3), 539–540 (2005).

13 Odom R. Rosacea, acne rosacea and actinic telangiectasia: in reply. *J. Am. Acad. Dermatol.* 53(6), 1103–1104 (2005).

14 Crawford GH, Pelle MT, James WD. Rosacea: I. Etiology, pathogenesis, and subtype classification. *J. Am. Acad. Dermatol.* 51(3), 327–341 (2004).

15 Izikson L, English JC III, Zirwas MJ. The flushing patient: differential diagnosis, workup, and treatment. *J. Am. Acad. Dermatol.* 55(2), 193–208 (2006).

16 Aloi F, Tomasini C, Soro E, Pippione M. The clinicopathologic spectrum of rhinophyma. *J. Am. Acad. Dermatol.* 42(3), 468–472 (2000).

17 Schechter BA, Katz RS, Friedman LS. Efficacy of topical cyclosporine for the treatment of ocular rosacea. *Adv. Ther.* 26(6), 651–659 (2009).

18 Gomaa AH, Yaar M, Eyada MMK, Bhawan J. Lymphangiogenesis and angiogenesis in non-phymatous rosacea. *J. Cutan. Pathol.* 34(10), 748–753 (2007).

19 Aroni K, Tsagroni E, Kavantzas N, Patsouris E, Ioannidis E. A study of the pathogenesis of rosacea: how angiogenesis and mast cells may participate in a complex multifactorial process. *Arch. Dermatol. Res.* 300(3), 125–131 (2008).

20 Abram K, Silm H, Maaroos HI, Oona M. Risk factors associated with rosacea. *J. Eur. Acad. Dermatol. Venereol.* 24(5) 565–571 (2009).

21 Yazici AC, Tamer L, Ikizoglu G *et al.* GSTM1 and GSTT1 null genotypes as possible heritable factors of rosacea. *Photodermatol. Photoimmunol. Photomed.* 22(4), 208–210 (2006).

22 Tan SR, Tope WD. Pulsed dye laser treatment of rosacea improves erythema, symptomatology, and quality of life. *J. Am. Acad. Dermatol.* 51(4), 592–599 (2004).

23 Lonne-Rahm S, Nordlind K, Edstrom DW, Ros A-M, Berg M. Laser treatment of rosacea: a pathoetiological study. *Arch. Dermatol.* 140(11), 1345–1349 (2004).

■ **Treatment of rosacea by pulsed dye laser decreased facial sensitivity and decreased substance P in the papillary dermis.**

24 Bamford JT. Rosacea: current thoughts on origin. *Semin. Cutan. Med. Surg.* 20(3), 199–206 (2001).

25 Millikan LE. Rosacea as an inflammatory disorder: a unifying theory? *Cutis.* 73(Suppl. 1), 5–8 (2004).

26 Zegarska B, Lelinska A, Tyrakowski T. Clinical and experimental aspects of cutaneous neurogenic inflammation. *Pharmacol. Rep.* 58(1), 13–21 (2006).

27 Powell FC, Corbally N, Powell D. Substance P and rosacea. *J. Am. Acad. Dermatol.* 28(1), 132–133 (1993).

28 Brain SD, Cox HM. Neuropeptides and their receptors: innovative science providing novel therapeutic targets. *Br. J. Pharmacol.* 147(Suppl. 1) S202–S211 (2006).

29 Peters EM, Ericson ME, Hosoi J *et al.* Neuropeptide control mechanisms in cutaneous biology: physiological and clinical significance. *J. Invest. Dermatol.* 126(9), 1937–1947 (2006).

30 Kohara H, Tajima S, Yamamoto M, Tabata Y. Angiogenesis induced by controlled release of neuropeptide substance P. *Biomaterials* 31(33), 8617–8625 (2010).

31 Lazaridou E, Apalla Z, Sotiraki S *et al.* Clinical and laboratory study of rosacea in northern Greece. *J. Eur. Acad. Dermatol. Venereol.* 24(4), 410–414 (2010).

32 Hirakawa S, Fujii S, Kajiya K, Yano K, Detmar M. Vascular endothelial growth factor promotes sensitivity to ultraviolet B-induced cutaneous photodamage. *Blood* 105(6), 2392–2399 (2005).

33 Kim MS, Kim YK, Eun HC, Cho KH, Chung JH. All-trans retinoic acid antagonizes UV-induced VEGF production and angiogenesis via the inhibition of ERK activation in human skin keratinocytes. *J. Invest. Dermatol.* 126(12), 2697–2706 (2006).

34 Chung JH, Eun HC. Angiogenesis in skin aging and photoaging. *J. Dermatol.* 34(9), 593–600 (2007).

35 Scholzen TE, Brzoska T, Kalden DH *et al.* Effect of ultraviolet light on the release of neuropeptides and neuroendocrine hormones in the skin: mediators of photodermatitis and cutaneous inflammation. *J. Investig. Dermatol. Symp. Proc.* 4(1), 55–60 (1999).

36 Bernstein EF, Chen YQ, Kopp JB *et al.* Long-term sun exposure alters the collagen of the papillary dermis. Comparison of sun-protected and photoaged skin by northern analysis, immunohistochemical staining, and confocal laser scanning microscopy. *J. Am. Acad. Dermatol.* 34(2), 209–218 (1996).

37 Quan T, Qin Z, Xia W *et al.* Matrix-degrading metalloproteinases in photoaging. *J. Investig. Dermatol. Symp. Proc.* 14(1), 20–24 (2009).

38 Varani J, Perone P, Warner RL *et al.* Vascular tube formation on matrix metalloproteinase-1-damaged collagen. *Br. J. Cancer* 98(10), 1646–1652 (2008).

39 McAleer MA, Fitzpatrick P, Powell FC. Papulopustular rosacea: prevalence and relationship to photodamage. *J. Am. Acad. Dermatol.* 63(1), 33–39 (2010).

40 Bae YI, Yun SJ, Lee JB *et al.* Clinical evaluation of 168 Korean patients with rosacea: the sun exposure correlates with the erythematotelangiectatic subtype. *Ann. Dermatol.* 21(3), 243–249 (2009).

41 Jang YH, Sim JH, Kang HY, Kim YC, Lee ES. Immunohistochemical expression of matrix metalloproteinases in the granulomatous rosacea compared with the non-granulomatous rosacea. *J. Eur. Acad. Dermatol. Venereol.*DOI: 10.1111/j.1468-3083.2010.03825.x (2010).

42 Bakar O, Demircay Z, Yuksel M, Haklar G, Sanisoglu Y. The effect of azithromycin on reactive oxygen species in rosacea. *Clin. Exp. Dermatol.* 32(2), 197–200 (2007).

43 Bickers DR, Athar M. Oxidative stress in the pathogenesis of skin disease. *J. Invest. Dermatol.* 126(12), 2565–2575 (2006).

44 Heck DE, Gerecke DR, Vetrano AM, Laskin JD. Solar ultraviolet radiation as a trigger of cell signal transduction. *Toxicol. Appl. Pharmacol.* 195(3), 288–297 (2004).

45 Wlaschek M, Briviba K, Stricklin GP, Sies H, Scharffetter-Kochanek K. Singlet oxygen may mediate the ultraviolet A-induced synthesis of interstitial collagenase. *J. Invest. Dermatol.* 104(2), 194–198 (1995).

46 Öztas MO, Balk M, Ögüs E *et al.* The role of free oxygen radicals in the aetiopathogenesis of rosacea. *Clin. Exp. Dermatol.* 28(2), 188–192 (2003).

47 Tisma VS, Basta-Juzbasic A, Jaganjac M *et al.* Oxidative stress and ferritin expression in the skin of patients with rosacea. *J. Am. Acad. Dermatol.* 60(2), 270–276 (2009).

48 Zhao YE, Wu LP, Peng Y, Cheng H. Retrospective analysis of the association between Demodex infestation and rosacea. *Arch. Dermatol.* 146(8), 896–902 (2010).

49 Kocak M, Yagli S, Vahapoglu G, Eksioglu M. Permethrin 5% cream versus metronidazole 0.75% gel for the treatment of papulopustular rosacea. A randomized double-blind placebo-controlled study. *Dermatology* 205(3), 265–270 (2002).

50 Allen KJ, Davis CL, Billings SD, Mousdicas N. Recalcitrant papulopustular rosacea in an immunocompetent patient responding to combination therapy with oral ivermectin and topical permethrin. *Cutis.* 80(2), 149–151 (2007).

51 Elston DM. Demodex mites: facts and controversies. *Clin. Dermatol.* 28(5), 502–504 (2010).

52 Hsu CK, Hsu MM, Lee JY. Demodicosis: a clinicopathological study. *J. Am. Acad. Dermatol.* 60(3), 453–462 (2009).

53 Bonnar E, Eustace P, Powell FC. The Demodex mite population in rosacea. *J. Am. Acad. Dermatol.* 28(3), 443–448 (1993).

54 Ozturkcan S, Ermertcan AT, Sahin MT, Afsar FS. Efficiency of benzoyl peroxide-erythromycin gel in comparison with metronidazole gel in the treatment of acne rosacea. *J. Dermatol.* 31(8), 610–617 (2004).

55 Georgala S, Katoulis AC, Kylafis GD *et al.* Increased density of Demodex folliculorum and evidence of delayed hypersensitivity reaction in subjects with papulopustular rosacea. *J. Eur. Acad. Dermatol. Venereol.* 15(5), 441–444 (2001).

56 Lacey N, Delaney S, Kavanagh K, Powell FC. Mite-related bacterial antigens stimulate inflammatory cells in rosacea. *Br. J. Dermatol.* 157(3), 474–481 (2007).

57 Li J, O'Reilly N, Sheha H *et al.* Correlation between ocular Demodex infestation and serum immunoreactivity to Bacillus proteins in patients with facial rosacea. *Ophthalmology* 117(5), 870–877 (2010).

58 Meylan E, Tschopp J, Karin M. Intracellular pattern recognition receptors in the host response. *Nature* 442(7098), 39–44 (2006).

59 Yamasaki K, Kanada K, Macleod DT *et al.* TLR2 expression is increased in rosacea and stimulates enhanced serine protease production by keratinocytes. *J. Invest. Dermatol.* 131(3), 688–697 (2011).

60 Yamasaki K, Di Nardo A, Bardan A *et al.* Increased serine protease activity and cathelicidin promotes skin inflammation in rosacea. *Nat. Med.* 13(8), 975–980 (2007).

■■ **The proinflammatory form of cathelicidin, LL-37 and stratum corneum trypic enzyme (kallikrein 5) are elevated in rosacea skin. This is a landmark study implicating dysregulation of the innate immune system in rosacea pathogenesis.**

61 Rothe MJ, Nowak M, Kerdel FA. The mast cell in health and disease. *J. Am. Acad. Dermatol.* 23(4), 615–624 (1990).

62 Iddamalgoda A, Le QT, Ito K *et al.* Mast cell tryptase and photoaging: possible involvement in the degradation of extra cellular matrix and basement membrane proteins. *Arch. Dermatol. Res.* 300(Suppl. 1) S69–S76 (2008).

63 van Zuuren EJ, Gupta AK, Gover MD, Graber M, Hollis S. Systematic review of rosacea treatments. *J. Am. Acad. Dermatol.* 56(1), 107–115 (2007).

64 Laquieze S, Czernielewski J, Baltas E. Beneficial use of Cetaphil moisturizing cream as part of a daily skin care regimen for individuals with rosacea. *J. Dermatolog. Treat.* 18(3), 158–162 (2007).

65 Del Rosso JQ. The use of moisturizers as an integral component of topical therapy for rosacea: clinical results based on the assessment of skin characteristics study. *Cutis.* 84(2), 72–76 (2009).

66 Dirschka T, Tronnier H, Folster-Holst R. Epithelial barrier function and atopic diathesis in rosacea and perioral dermatitis. *Br. J. Dermatol.* 150(6), 1136–1141 (2004).

67 Dorschner RA, Pestonjamasp VK, Tamakuwala S *et al.* Cutaneous injury induces the release of cathelicidin anti-microbial peptides active against group A Streptococcus. *J. Invest. Dermatol.* 117(1), 91–97 (2001).

68 Draelos ZD. Facial hygiene and comprehensive management of rosacea. *Cutis.* 73(3), 183–187 (2004).

69 Dahl MV, Katz HI, Krueger GG *et al.* Topical metronidazole maintains remissions of rosacea. *Arch. Dermatol.* 134(6), 679–683 (1998).

70 Jorizzo JL, Lebwohl M, Tobey RE. The efficacy of metronidazole 1% cream once daily compared with metronidazole 1% cream twice daily and their vehicles in rosacea: a double-blind clinical trial. *J. Am. Acad. Dermatol.* 39(3), 502–504 (1998).

■■ **Randomized double-blind clinical trial that establishes topical metronidazole as an effective therapy for papulopustular rosacea.**

71 Miyachi Y. Potential antioxidant mechanism of action for metronidazole: implications for rosacea management. *Adv. Ther.* 18(6), 237–243 (2001).

72 Narayanan S, Hunerbein A, Getie M, Jackel A, Neubert RH. Scavenging properties of metronidazole on free oxygen radicals in a skin lipid model system. *J. Pharm. Pharmacol.* 59(8), 1125–1130 (2007).

73 Yoo J, Reid DC, Kimball AB. Metronidazole in the treatment of rosacea: do formulation, dosing, and concentration matter? *J. Drugs Dermatol.* 5(4), 317–319 (2006).

74 Gupta AK, Nicol K. The use of sulfur in dermatology. *J. Drugs Dermatol.* 3(4), 427–431 (2004).

75 Abramovits W, Kennedy AJ. Sulfur/sodium sulfacetamide preparations. *Skinmed* 3(2), 95–101 (2004).

76 Sauder DN, Miller R, Gratton D *et al.* The treatment of rosacea: the safety and efficacy of sodium sulfacetamide 10% and sulfur 5% lotion (Novacet) is demonstrated in a double blind study. *J. Dermatolog. Treat.* 8 79–85 (1997).

77 Trumbore MW, Goldstein JA, Gurge RM. Treatment of papulopustular rosacea with sodium sulfacetamide 10%/sulfur 5% emollient foam. *J. Drugs Dermatol.* 8(3), 299–304 (2009).

78 Torok HM, Webster G, Dunlap FE *et al.* Combination sodium sulfacetamide 10% and sulfur 5% cream with sunscreens versus metronidazole 0.75% cream for rosacea. *Cutis.* 75(6), 357–363 (2005).

79 Lebwohl M, Medansky R, Russo C, Plott R. The comparative efficacy of sodium sulfacetamide 10%/sulfur 5% (Sulfacet-R) lotion and metronidazole 0.75% (MetroGel) in the treatment of rosacea. *J. Geriatr. Dermatol.* 3, 183–185 (1995).

80 Mills OH Jr, Kligman AM. Letter: topically applied erythromycin in rosacea. *Arch. Dermatol.* 112(4), 553–554 (1976).

81 Wilkin JK, DeWitt S. Treatment of rosacea: topical clindamycin versus oral tetracycline. *Int. J. Dermatol.* 32(1), 65–67 (1993).

82 Montes LF, Cordero AA, Kriner J, Loder J, Flanagan AD. Topical treatment of acne rosacea with benzoyl peroxide acetone gel. *Cutis.* 32(2), 185–190 (1983).

83 Breneman D, Savin R, VandePol C *et al.* Double-blind, randomized, vehicle-controlled clinical trial of once-daily benzoyl peroxide/clindamycin topical gel in the treatment of patients with moderate to severe rosacea. *Int. J. Dermatol.* 43(5), 381–387 (2004).

84 Leyden JJ, Thiboutot D, Shalita A. Photographic review of results from a clinical study comparing benzoyl peroxide 5%/clindamycin 1% topical gel with vehicle in the treatment of rosacea. *Cutis.* 73(Suppl. 6), 11–17 (2004).

85 Liu RH, Smith MK, Basta SA, Farmer ER. Azelaic acid in the treatment of papulopustular rosacea: a systematic review of randomized controlled trials. *Arch. Dermatol.* 142(8), 1047–1052 (2006).

86 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.* 48(6), 836–845 (2003).

■■ **Establishes topical azelaic acid as an effective therapy for papulopustular rosacea.**

87 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.* 79(6), 456–459 (1999).

88 Elewski BE, Fleischer AB Jr, Pariser DM. A comparison of 15% azelaic acid gel and 0.75% metronidazole gel in the topical treatment of papulopustular rosacea: results of a randomized trial. *Arch. Dermatol.* 139(11), 1444–1450 (2003).

89 Akamatsu H, Komura J, Asada Y, Miyachi Y, Niwa Y. Inhibitory effect of azelaic acid on neutrophil functions: a possible cause for its efficacy in treating pathogenetically unrelated diseases. *Arch. Dermatol. Res.* 283(3), 162–166 (1991).

90 Pelle MT, Crawford GH, James WD. Rosacea: II. Therapy. *J. Am. Acad. Dermatol.* 51(4), 499–512 (2004).

91 Conde JF, Yelverton CB, Balkrishnan R, Fleischer AB Jr, Feldman SR. Managing rosacea: a review of the use of metronidazole alone and in combination with oral antibiotics. *J. Drugs Dermatol.* 6(5), 495–498 (2007).

92 Sneddon IB. A clinical trial of tetracycline in rosacea. *Br. J. Dermatol.* 78(12), 649–652 (1966).

93 Khokhar O, Khachemoune A. A case of granulomatous rosacea: sorting granulomatous rosacea from other granulomatous diseases that affect the face. *Dermatol. Online J.* 10(1), 6 (2004).

94 Ochsendorf F. Systemic antibiotic therapy of acne vulgaris. *J. Dtsch. Dermatol. Ges.* 4(10), 828–841 (2006).

95 Korting HC, Schollmann C. Tetracycline actions relevant to rosacea treatment. *Skin Pharmacol. Physiol.* 22(6), 287–294 (2009).

96 Bender A, Zapolanski T, Watkins S *et al.* Tetracycline suppresses ATP γ S-induced CXCL8 and CXCL1 production by the human dermal microvascular endothelial cell-1 (HMEC-1) cell line and primary human dermal microvascular endothelial cells. *Exp. Dermatol.* 17(9), 752–760 (2008).

97 Uitto VJ, Firth JD, Nip L, Golub LM. Doxycycline and chemically modified tetracyclines inhibit gelatinase A (MMP-2) gene expression in human skin keratinocytes. *Ann. NY Acad. Sci.* 732, 140–151 (1994).

98 Sanchez J, Somolinos AL, Almodóvar PI *et al.* A randomized, double-blind, placebo-controlled trial of the combined effect of doxycycline hyclate 20-mg tablets and metronidazole 0.75% topical lotion in the treatment of rosacea. *J. Am. Acad. Dermatol.* 53(5), 791–797 (2005).

99 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.* 56(5), 791–802 (2007).

■■ **Establishes anti-inflammatory dose doxycycline as an effective therapy for papulopustular rosacea.**

100 Del Rosso JQ, Leyden JJ, Thiboutot D, Webster GF. Antibiotic use in acne vulgaris and rosacea: clinical considerations and resistance issues of significance to dermatologists. *Cutis.* 82(Suppl. 2), 5–12 (2008).

101 Del Rosso JQ, Bruce S, Jarratt M, Menter A, Staedtler G. Efficacy of topical azelaic acid (AzA) gel 15% plus oral doxycycline 40 mg versus metronidazole gel 1% plus oral doxycycline 40 mg in mild-to-moderate papulopustular rosacea. *J. Drugs Dermatol.* 9(6), 607–613 (2010).

102 Torresani C, Pavesi A, Manara GC. Clarithromycin versus doxycycline in the treatment of rosacea. *Int. J. Dermatol.* 36(12), 942–946 (1997).

103 Bakar O, Demircay Z, Gurbuz O. Therapeutic potential of azithromycin in rosacea. *Int. J. Dermatol.* 43(2), 151–154 (2004).

104 Cetinkaya A, Akova YA. Pediatric ocular acne rosacea: long-term treatment with systemic antibiotics. *Am. J. Ophthalmol.* 142(5), 816–821 (2006).

105 Akhyani M, Ehsani AH, Ghiasi M, Jafari AK. Comparison of efficacy of azithromycin vs doxycycline in the treatment of rosacea: a randomized open clinical trial. *Int. J. Dermatol.* 47(3), 284–288 (2008).

106 Levert H, Gressier B, Moutard I *et al.* Azithromycin impact on neutrophil oxidative metabolism depends on exposure time. *Inflammation* 22(2), 191–201 (1998).

107 Kadota J, Iwashita T, Matsubara Y *et al.* Inhibitory effect of erythromycin on superoxide anion production by human neutrophils primed with granulocyte-colony stimulating factor. *Antimicrob. Agents Chemother.* 42(7), 1866–1867 (1998).

108 Saihan EM, Burton JL. A double-blind trial of metronidazole versus oxytetracycline therapy for rosacea. *Br. J. Dermatol.* 102(4), 443–445 (1980).

109 Kang S. The mechanism of action of topical retinoids. *Cutis.* 75(Suppl. 2), 10–13 (2005).

110 Liu PT, Krutzik SR, Kim J, Modlin RL. Cutting edge: all-trans retinoic acid down-regulates TLR2 expression and function. *J. Immunol.* 174(5), 2467–2470 (2005).

111 Ertl GA, Levine N, Kligman AM. A comparison of the efficacy of topical tretinoin and low-dose oral isotretinoin in rosacea. *Arch. Dermatol.* 130(3), 319–324 (1994).

112 Altinyazar HC, Koca R, Tekin NS, Esturk E. Adapalene vs metronidazole gel for the treatment of rosacea. *Int. J. Dermatol.* 44(3), 252–255 (2005).

113 Vienne MP, Ochando N, Borrel MT *et al.* Retinaldehyde alleviates rosacea. *Dermatology* 199(Suppl. 1) 53–56 (1999).

114 Green LJ, McCormick A, Weinstein GD. Photoaging and the skin. The effects of tretinoin. *Dermatol. Clin.* 11(1), 97–105 (1993).

115 Merritt B, Burkhart CN, Morrell DS. Use of isotretinoin for acne vulgaris. *Pediatr. Ann.* 38(6), 311–320 (2009).

116 Nelson AM, Zhao W, Gilliland KL *et al.* Temporal changes in gene expression in the skin of patients treated with isotretinoin provide insight into its mechanism of action. *Dermatoendocrinol.* 1(3), 177–187 (2009).

117 Hoting E, Paul E, Plewig G. Treatment of rosacea with isotretinoin. *Int. J. Dermatol.* 25(10), 660–663 (1986).

118 Turjanmaa K, Reunala T. Isotretinoin treatment of rosacea. *Acta Derm. Venereol.* 67(1), 89–91 (1987).

119 Plewig G, Nikolowski J, Wolff HH. Action of isotretinoin in acne rosacea and gram-negative folliculitis. *J. Am. Acad. Dermatol.* 6(4), 766–785 (1982).

120 Gollnick H, Blume-Peytavi U, Szabo EL *et al.* Systemic isotretinoin in the treatment of rosacea – doxycycline- and placebo-controlled, randomized clinical study. *J. Dtsch. Dermatol. Ges.* 8(7), 505–515 (2010).

121 Erdogan FG, Yurtsever P, Aksoy D, Eskioglu F. Efficacy of low-dose isotretinoin in patients with treatment-resistant rosacea. *Arch. Dermatol.* 134(7), 884–885 (1998).

122 Mostafa FF, El Harras MA, Gomaa SM *et al.* Comparative study of some treatment modalities of rosacea. *J. Eur. Acad. Dermatol. Venereol.* 23(1), 22–28 (2009).

123 Guarrera M, Parodi A, Cipriani C, Divano C, Rebora A. Flushing in rosacea: a possible mechanism. *Arch. Dermatol. Res.* 272(3–4), 311–316 (1982).

124 Craige H, Cohen JB. Symptomatic treatment of idiopathic and rosacea-associated cutaneous flushing with propranolol. *J. Am. Acad. Dermatol.* 53(5), 881–884 (2005).

125 Wilkin JK. Effect of subdepressor clonidine on flushing reactions in rosacea. Change in malar thermal circulation index during provoked flushing reactions. *Arch. Dermatol.* 119(3), 211–214 (1983).

126 Wilkin JK. Effect of nadolol on flushing reactions in rosacea. *J. Am. Acad. Dermatol.* 20(2), 202–205 (1989).

127 Rada G, Capurro D, Pantoja T *et al.* Non-hormonal interventions for hot flushes in women with a history of breast cancer. *Cochrane Database Syst. Rev.* (9), CD004923 (2010).

128 Beck-Speier I, Dayal N, Karg E *et al.* Oxymetazoline inhibits proinflammatory reactions: effect on arachidonic acid-derived metabolites. *J. Pharmacol. Exp. Ther.* 316(2), 843–851 (2006).

129 Beck-Speier I, Oswald B, Maier KL, Karg E, Ramseger R. Oxymetazoline inhibits and resolves inflammatory reactions in human neutrophils. *J. Pharmacol. Sci.* 110(3), 276–284 (2009).

130 Shanler SD, Ondo AL. Successful treatment of the erythema and flushing of rosacea using a topically applied selective α1-adrenergic receptor agonist, oxymetazoline. *Arch. Dermatol.* 143(11), 1369–1371 (2007).

■ **Case reports of decreased erythema and symptoms of erythematotelangiectatic rosacea with the use of the topical vasoconstrictor oxymetazoline.**

131 Shanler S, Ondo A. Successful treatment of the erythema and flushing of rosacea using a topically applied selective α1 adrenergic receptor agonist, oxymetazoline. Presented at: *The American Academy of Dermatology 66th Annual Meeting.* San Antonio, TX, USA, 1–5 February 2008.

132 Lowe NJ, Behr KL, Fitzpatrick R, Goldman M, Ruiz-Esparza J. Flash lamp pumped dye laser for rosacea-associated telangiectasia and erythema. *J. Dermatol. Surg. Oncol.* 17(6), 522–525 (1991).

133 Tan ST, Bialostocki A, Armstrong JR. Pulsed dye laser therapy for rosacea. *Br. J. Plast. Surg.* 57(4), 303–310 (2004).

134 Neuhaus IM, Zane LT, Tope WD. Comparative efficacy of nonpurpuragenic pulsed dye laser and intense pulsed light for erythematotelangiectatic rosacea. *Dermatol. Surg.* 35(6), 920–928 (2009).

135 Butterwick KJ, Butterwick LS, Han A. Laser and light therapies for acne rosacea. *J. Drugs Dermatol.* 5(1), 35–39 (2006).

136 Papageorgiou P, Clayton W, Norwood S, Chopra S, Rustin M. Treatment of rosacea with intense pulsed light: significant improvement and long-lasting results. *Br. J. Dermatol.* 159(3), 628–632 (2008).

137 Taub AF. Treatment of rosacea with intense pulsed light. *J. Drugs Dermatol.* 2(3), 254–259 (2003).

138 Angermeier MC. Treatment of facial vascular lesions with intense pulsed light. *J. Cutan. Laser Ther.* 1(2), 95–100 (1999).

139 Schroeter CA, Haaf-von Below S, Neumann HA. Effective treatment of rosacea using intense pulsed light systems. *Dermatol. Surg.* 31(10), 1285–1289 (2005).

140 Madan V, Ferguson JE, August PJ. Carbon dioxide laser treatment of rhinophyma: a review of 124 patients. *Br. J. Dermatol.* 161(4), 814–818 (2009).

141 Tahery J, Zakaria R, Natt RS. Diode laser treatment of rhinophyma. *Clin. Otolaryngol.* 35(5), 442–444 (2010).

142 Apikian M, Goodman GJ, Roberts S. Management of mild to moderate rhinophyma with a 1,450-nm diode laser: report of five patients. *Dermatol. Surg.* 33(7), 847–850 (2007).

143 Halsbergen Henning JP, van Gemert MJ. Rhinophyma treated by argon laser. *Lasers Surg. Med.* 2(3), 211–215 (1983).

144 Kempiak SJ, Lee PW, Pelle MT. Rhinophyma treated with cryosurgery. *Dermatol. Surg.* 35(3), 543–545 (2009).

145 Sadick H, Goepel B, Bersch C *et al.* Rhinophyma: diagnosis and treatment options for a disfiguring tumor of the nose. *Ann. Plast. Surg.* 61(1), 114–120 (2008).

146 Wolf JE Jr, Del Rosso JQ. The CLEAR trial: results of a large community-based study of metronidazole gel in rosacea. *Cutis.* 79(1), 73–80 (2007).

147 Thiboutot DM, Fleischer AB, Del Rosso JQ, Rich P. A multicenter study of topical azelaic acid 15% gel in combination with oral doxycycline as initial therapy and azelaic acid 15% gel as maintenance monotherapy. *J. Drugs Dermatol.* 8(7), 639–648 (2009).

148 Tanzi EL, Weinberg JM. The ocular manifestations of rosacea. *Cutis.* 68(2), 112–114 (2001).

149 Barnhorst DA Jr, Foster JA, Chern KC, Meisler DM. The efficacy of topical metronidazole in the treatment of ocular rosacea. *Ophthalmology* 103(11), 1880–1883 (1996).

150 Krause MH, Torricelli R, Kundig T, Trueb RM, Hafner J. [Dapsone in granulomatous rosacea]. *Hautarzt.* 48(4), 246–248 (1997).

151 Cunha PR, Rossi AB. Pimecrolimus cream 1% is effective in a case of granulomatous rosacea. *Acta Derm. Venereol.* 86(1), 71–72 (2006).

152 Gul U, Gonul M, Kilic A *et al.* A case of granulomatous rosacea successfully treated with pimecrolimus cream. *J. Dermatolog. Treat.* 19(5), 313–315 (2008).

Websites

201 National Rosacea Society. Rosacea review. Rosacea now estimated to affect at least 16 million Americans www.rosacea.org/rr/2010/winter/article_1.php 2010 (Accessed 28 December 2010)

202 National Rosacea Society. Rosacea review. Survey shows rosacea's emotional toll, positive effects of medical therapy www.rosacea.org/rr/2007/spring/article_3.php. 2007 (Accessed 28 December 2010)