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Review Article

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Challenges and Advances in Rosacea Management

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Abstract

Rosacea is a common chronic inflammatory disorder characterized by symptoms of facial flushing and spectrums of clinical signs, including erythema, dry skin, and an inflammatory papulopustular eruption with periods of exacerbation. The current classification system developed by the National Rosacea Society Expert Committee consists of erythematotelangiectatic, papulopustular, phymatous, and ocular subtypes. Individual subtypes are likely a result of different pathogenic factors and respond best to different therapeutic regimens. Before initiation of therapy, the triggering factors should be identified and avoided. Daily applied sunscreen is a must. The main treatment modalities for rosacea include topical, systemic, laser, and light therapies. Traditional therapies include topical metronidazole or azelaic acid also oral therapy as tetracyclines or isotretinoin. Emerging therapies perhaps are more promising as topical ivermectin 1% cream which is proved to be safe and effective for the treatment of inflammatory lesions from papulopustular rosacea, Brimonidine tartrate and oxymetazoline are novel therapies to treat the erythema associated with rosacea. Other treatments as pimecrolimus 1% cream, clindamycin phosphate 1.2% + tretinoin 0.025% gel, pulsed dye laser and intense pulsed light can also be used. With the advent of novel therapeutic options for the treatment of rosacea such as subantimicrobial anti-inflammatory dose doxycycline, ivermectin and Brimonidine tartrate, there is renewed interest in the study of this disease which was once regarded as a debilitating disorder and now has become a well-known and manageable entity in the setting of these emerging therapeutic options. Herein, we describe the treatments currently available as well as the emerging and combination therapies.

Keywords: Rosacea, Erythematotelangiectatic, Papulopustular, Phymatous, Ivermectin, Oxymetazoline, Brimonidine

Introduction

Fascination with rosacea has been historically illustrated in medical art and literature, with imagery found in the Louvre dating back to the 15th century [1].

Rosacea is a common condition characterized by symptoms of facial flushing and a spectrum of clinical signs, including erythema, telangiectasia, coarseness of skin, and an inflammatory papulopustular eruption resembling acne [2].

Subtypes (based on specific clinical signs and described by the National Rosacea Society) Include Erythematotelangiectatic type, Papulopustular, Phymatous & Ocular types as well as other variants like granulomatous type which has also been presented [3].

Prevalence

The prevalence of rosacea ranges from 1% to 22% depending on the methodology and population sample analysed [4]. Generally, women are more often affected than men and rhinophyma is seen mostly in men over 40 years of age [5].

Differential Diagnosis

Understanding the clinical variants and disease course of rosacea is important to differentiate this entity from other conditions that can mimic rosacea. Facial disorders that may simulate individual presentations of rosacea include chronic photodamage; contact dermatitis; seborrheic dermatitis; systemic lupus erythematosus; dermatomyositis; Polymorphous Light Eruption; carcinoid syndrome [6].

Acne is commonly confused with rosacea, especially in middle-aged adults with late-onset acne. Telangiectasis is consistent with rosacea, but comedo formation is not. Eye symptoms are not associated with acne [7]. Steroid-induced acne presents with a more perioral distribution of the skin lesions [8].

To differentiate rosacea from Photodermatitis, malar rash of systemic lupus erythematosus, a skin biopsy may be necessary for a definitive diagnosis [9].

Aetiology and Pathogenesis

The pathophysiology of rosacea has undergone renewed interest over the past decade, with a large body of evidence supporting the role of an abnormal innate immune response. Many mechanisms interact with the cutaneous innate immune system that may be operative. A

variety of potential triggers stimulate this immune detection system which is upregulated and hyper-responsive in facial skin of patients with rosacea as compared to normal skin [10].

In innate immunity, the pattern recognition system, which includes the TLR (toll-like receptor) and NLR (nucleotide-binding domain and leucine-rich repeat-containing) families, respond to environmental stimuli such as UV, microbes, physical and chemical trauma. Triggering the innate immune system normally leads to a controlled increase in cytokines and antimicrobial molecules in the skin [11, 12].

One of these antimicrobial molecules is a peptide known as cathelicidin [13]. Individuals with rosacea expressed abnormally high levels of cathelicidin [14]. Importantly, the cathelicidin peptide forms found in rosacea were not only more abundant but were different from those in normal individuals. These forms of cathelicidin peptides promote and regulate leukocyte chemotaxis, angiogenesis and expression of extracellular matrix components [15-17].

Microbes and environmental changes, such as sun and UV exposure, would be sensed by innate immune systems through pattern recognition molecules. The innate immune systems would enhance and be enhanced by cytokine, reactive oxygen species (ROS), antimicrobial peptides, and proteases, which lead histological changes observed in rosacea. The multiple factors may heap up to cause rosacea clinical manifestations, while individual susceptibility to the factors is highly counted to cause rosacea. These new associations give us clues to further our understanding of the mechanisms responsible for the disease. Importantly, these advances also provide informed strategies for the optimal treatment of the clinical findings [18].

Psychological Factors

Rosacea patients have an increased risk of developing depression and anxiety and tend to avoid social situations. However, there are still limited data on this condition. Effective treatment of clinical symptoms brings significant improvement in psychological symptoms [19].

Treatment

Before the initiation of therapy, the triggering factors that exacerbate the patient's rosacea should be identified and avoided if possible. Common triggering factors include the following, Hot or cold temperature, Wind, Hot drinks, Caffeine, Exercise, Spicy food, Alcohol, Emotions, Topical products that irritate the skin and decrease the barrier and Medication that cause flushing. It is considered that an attempt to determine of triggering factors of rosacea should be the first step to treatment. Then it should be tried to eliminate contact with them [20].

A classification of rosacea has only limited value for initiating therapy, as in many cases combined forms of rosacea-typical symptoms are present. Therefore, treatment should be based less on classification but primarily on the symptoms. In rosacea flushing, persistent erythema, telangiectasia, papules with or without pustules, phymatous changes, and ocular manifestations can be defined as main symptoms. Burning, stinging, dry skin and localized or diffuse edema may occur as secondary diagnostic features.Primary objective of an adequate rosacea therapy is alleviation of these clinical manifestations and symptoms. For this purpose, diverse medical options can be chosen and combined with each another adapted to clinical manifestations and severity [21].

FDA Approved Treatments for Rosacea:

A: Topical treatment

Topical Metronidazole

Metronidazole is hypothesized to reduce oxidative stress and has proven effective in reducing erythema and inflammation [22].

No significant difference in clinical benefit was found using different vehicles (gel, cream, or lotion) or strengths (0.75% or 1%). Adverse effects were mild, including pruritus, irritation, and dryness [23].

Topical Azelaic Acid

Azelaic acid is a topical agent that has been approved by the U.S. Food and Drug Administration for the treatment of acne. It is available in a 20 percent cream base and appears to be safe and well tolerated [24].

A randomized, double-blinded study showed that azelaic acid was as effective as topical metronidazole in the treatment of pustular and papular forms of rosacea and had comparable side effects [25].

Metronidazole versus Azelaic Acid

Three studies assessed the effectiveness of metronidazole vs. azelaic acid. Although physician-assessed outcomes suggested that azelaic acid may be more effective than metronidazole, patient evaluations found no statistically significant differences. Azelaic acid had a higher incidence of adverse events, including dryness, stinging, scaling, itching, and burning. Symptoms were mild to moderate, and transient in both groups. Neither agent was found to be effective against telangiectasia [22].

Sulfacetamide/Sulfur

FDA approval of sulfacetamide/sulfur was granted primarily based on historical use before the implementation of more rigorous standards. Studies demonstrated effectiveness, but were also characterized by high or uncertain risk of bias [26].

B: Systemic therapy

Subantimicrobial Low-dose Oral Doxycycline

Standard antimicrobial dosing may affect endogenous flora and risks of the development of antibiotic resistant strains [27].

Thus modified-release doxycycline 40 mg once daily is the only systemic agent that is approved by the FDA for the treatment of papulopustular rosacea and provides anti-inflammatory effects with subantimicrobial dosing. The formulation allows for immediate release of 30 mg with delayed release of 10 mg once ingested [28].

Through inhibition of numerous matrix metalloproteinases, a reduction in the quantity and activity of serine protease kallikrein 5 results in decreased production of cathelicidin LL-37, the same antimicrobial peptide (AMP) that has been highlighted in the pathogenesis of rosacea [29].

Key anti-inflammatory actions of doxycycline in rosacea include: downregulation of cytokines, reducing neutrophil infiltration, inhibition of nitric oxide and its vasodilatory effects, reduction of reactive oxygen species, slowing connective tissue destruction, and

inhibition of matrix metalloproteinases [30].

In a small, randomized, double-blind trial, no additional improvement in rosacea symptoms was achieved with oral doxycycline 100 mg once daily [31].

C: Emerging Topically applied therapies:

Ivermectin cream

Developed from the naturally occurring antiparasitic compound avermectin [32].

A phase 3 randomized, double-blind, 12-week vehicle-controlled, parallel-group study assessing the efficacy and safety of ivermectin 1% cream versus vehicle cream in subjects with papulopustular rosacea and a comparator extension phase for 40 weeks as a long-term extension with Ivermectin 1% cream or azelaic acid 15% gel (safety study)has demonstrated that ivermectin 1% cream was safe and effective for the treatment of inflammatory lesions from papulopustular rosacea [33,34].

Efficacy and safety of ivermectin 1% cream vs metronidazole 0.75% cream in subjects with papulopustular rosacea over 16 weeks of treatment, followed by a 36-week extension period found that ivermectin was slightly more effective than topical metronidazole in patient- and physician-assessed outcomes and quality of life [35].

Brimonidine and Oxymetazoline

Novel therapies to treat the erythema associated with rosacea have been developed and have the potential to fill a void in the arsenal of rosacea therapeutics brimonidine tartrate and oxymetazoline, which have potent vasoconstrictive activity and anti-redness capabilities, were first found in eye drops for glaucoma and a nasal decongestant spray, respectively [36].

Brimonidine tartrate

Brimonidine tartrate, an alpha-2 agonist, has been shown in a two part dose-finding Phase II study to be safe and efficacious in reducing the erythema of rosacea. A single application of the 0.5% gel reduced erythema between 30 minutes to 12 hours, as measured with an objective chromameter [37].

In part B of the study, two dosages (0.18% and 0.5%) of the gel was compared to vehicle over a 4 week period in 269 subjects. No tachyphylaxis, aggravation of symptoms or rebound erythema was observed. The majority of adverse effects were skin-related and mild and transient in nature. The 0.5% gel once daily was significantly more effective according to both patient and clinician assessments [36].

Oxymetazoline

The topical α-agonist, oxymetazoline, is safe and effective for reducing persistent facial redness associated with erythematotelangiectatic subtype of rosacea [38].

In the Pivotal Trial of the Efficacy and Safety of Oxymetazoline Cream 1.0% for the treatment of Persistent Facial Erythema Associated With Rosacea, Topical oxymetazoline applied to the face once daily for 29 days was proven to be effective, safe, and well tolerated in the treatment of moderate to severe persistent facial erythema of rosacea [39].

Off-label therapies:

Systemic isotretinoin

Systemic isotretinoin has also been used off-label in the treatment of patients with severe rosacea. A randomized, double-blind trial, comparing the use of different dosages of oral isotretinoin to both doxycycline and placebo found isotretinoin 0.3 mg/kg to be an effective therapy with a similar safety profile as for the treatment of acne [40].

Topical retinoids

Topical retinoids, in particularly adapalene, have been used as an alternative management of papulopustular rosacea mainly because of their anti-inflammatory and keratolytic effects. Compared with metronidazole 0.75 % gel, topical adapalene 0.1 % gel has been more effective treating inflammatory lesions but showed no significant difference in erythema or telangiectasia improvement [41].

Oral ivermectin and topical permethrin

Reports have been published on cutaneous demodicidosis responding to oral ivermectin and topical permethrin [42].

Topical calcineurin inhibitors

Due to their anti-inflammatory properties, topical calcineurin inhibitors like 0.1 % tacrolimus ointment and 1 % pimecrolimus cream have been investigated for use in papulopustular rosacea with heterogeneous results. An open-label randomized trial with pimecrolimus 1 % cream applied over four weeks revealed a significant reduction in rosacea clinical scores at the end of the pimecrolimus treatment ($p < 0.05$) [43].

In addition, the open-label application of 0.1 % tacrolimus topical ointment over twelve weeks significantly improved the erythema in patients with erythematotelangiectatic or papulopustular rosacea subtypes ($p < 0.05$), although there was no decrease in the number of papulopustular lesions [44].

Antibiotic and tretinoin preparations

Various topical regimens including an antibiotic and tretinoin preparations have been proposed. A recent randomized, doubleblind, placebo-controlled study assessing a combination gel of clindamycin phosphate 1.2% + tretinoin 0.025% found no difference in papule/pustule count, but mild improvement in the telangiectatic component of rosacea was observed [45].

Pulsed dye laser and intense pulsed light

In a randomized, controlled, single-blind, split-face trial of patients with erythematotelangiectatic rosacea, both pulsed dye laser and intense pulsed light treatments were found to have similar efficacy and safety [46,47].

Oral zinc sulfate

Finally, oral zinc sulfate has been proposed as an additional oral treatment for rosacea. In a randomized, controlled, double-blind, crossover study of 19 patients receiving 100 mg zinc sulfate capsules or placebo three times daily, significantly reduced scores were seen in both treatment arms during the zinc treatment arm, with a relative plateau during the placebo phase [48].

In contrast, a similar trial of 220 mg zinc sulfate dosed twice daily showed no difference in patients receiving zinc therapy versus placebo [49].

Therapy for Phymatous Rosacea

Phymatous rosacea can be disfiguring and difficult to treat. Best results are achieved when treatment is instituted early. Oral isotretinoin may be effective in reducing nasal volume in early disease; however, recurrence is likely after discontinuation, and mucinous and fibrotic changes are unresponsive [50,51].

Surgical techniques including laser- or light-based therapies (pulsed dye laser, intense pulsed light, carbon dioxide laser), electrosurgery, dermabrasion, tangential excision, electroscalpel, loop cautery, and scissor sculpting are effective in correcting or minimizing phymatous changes and may be life-changing [50,52].

Conclusion

Now with the presence of the newly introduced drugs and modalities for the treatment of rosacea, once considered as a debilitating disease, there is a new hope for a better management of the condition together with improvement of the phycological impact on the affected patients. Better understanding of the pathophysiology of rosacea gives a wider range of options for the management as well. The promising newly therapeutic treatments as subantimicrobial anti-inflammatory dose doxycycline, ivermectin and the alpha-adrenergic receptor agonists, opens the way to study further therapeutic options of the disease. It is required to to consider a well-designed, high-quality studies for the other treatment options of rosacea which are not yet approved and the widely used off-label therapies that appear to be useful such as systemic isotretinoin, permethrin, topical retinoids, and topical calcineurin inhibitors. Comparative studies of the emergent therapies with other modalities are also required for better treatment results. On every occasion, the decision of choosing the proper treatment option should be based on the symptoms of rosacea, the patient condition & compliance as well as the experience of the physician with a solid background of a highly validated studies and the knowledge of the newly introduced treatment options to achieve the highest possible outcomes.

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