ARTICLES

ROSACEA: WHERE ARE WE NOW?

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Abstract

Advances continue to be made in the classification and treatment of rosacea, a chronic dermatologic syndrome. A new empiric classification system identifies 4 rosacea subtypes (erythematotelangiectatic, papulopustular, phymatous, and ocular) that may aid in more precise diagnosis. Several new therapies have recently been approved for treatment of rosacea. Azelaic acid 15% gel is a new first-tier topical agent proven effective in reducing inflammatory lesions and erythema. New formulations of metronidazole and sulfacetamide 10%/sulfur 5% that offer cosmetic or tolerability advantages are now available. Intense pulsed light therapy has demonstrated effectiveness in reducing flushing, erythema, and telangiectases, with greater tolerability than existing laser systems. Other treatments under investigation include low-dose doxycycline hyclate (which may provide greater safety than existing oral antibiotics), benzoyl peroxide/clindamycin gel, and tacrolimus ointment (for steroid-induced rosacea). With this expanded armamentarium of medical and light-based therapies, clinicians can now implement a multifaceted approach to treatment, crafting new treatment combinations to address the unique and evolving features of rosacea in each individual patient.

Introduction

To date, there is no clearly identified cause for rosacea and no recognized cure[1-4]. Rosacea is a condition that is managed. For many of the 14 million Americans diagnosed with this dermatologic syndrome, the marked stigmata of rosacea contribute to low self-esteem, stress on the job, and social isolation[4,5]. Thus, the paramount goal of all rosacea management strategies must be to improve quality of life for patients. Fortunately, new advances in the understanding of rosacea and an expanding array of treatment options are making it possible to more finely tune treatment to address the individual needs of each patient, leading to improved outcomes. This article will review advances in the classification and treatment of rosacea that have occurred over the last few years and will suggest a multifaceted approach to treatment of each recognized subtype of rosacea.

A More Precise Classification System

Rosacea is not a disease but rather a syndrome with an individual presentation in each patient[1]. Most patients experience flushing and/or erythema; many present with inflammatory papules and pustules, edema, telangiectasia, or ocular symptoms; a few (mostly men) develop rhinophyma[1,3]. In each patient, these characteristic signs and symptoms appear in different configurations that often change over time, as flare-ups interrupt periods of remission[1,3]. Historically, rosacea has been described in terms of 4 stages: prerosacea (intermittent episodes of flushing or blushing); stage 1 (erythema persisting for hours or days and tiny telangiectases); stage 2 (inflammatory papules and pustules, persistent erythema, more telangiectasia); and stage 3 (moderate to severe erythema, inflammatory lesions, and/or telangiectasia, appearance of phymas)[1,3-7]. Many practitioners, as well as the published literature and clinical trial evaluations, continue to rely on this staging system. However, stages imply a progressive disease course, suggesting that flushing leads to persistent erythema, then eventually to the appearance of inflammatory lesions, worsening telangiectasia, and in some cases phymatous growth. This evolutionary progression, while observed in some patients, is not congruent with clinical findings by dermatologists in many patients.

A standard, empiric classification system, developed by an expert committee of the National Rosacea Society and published in 2002, aims to establish a more scientifically precise paradigm for diagnosis of rosacea[2]. Because there is no clear etiology or pathogenesis of rosacea, the classification is based on morphologic characteristics. Four primary features of rosacea are identified: flushing, nontransient erythema, papules and pustules, and telangiectasia. At least 1 of these features, with a central face distribution, is required for a diagnosis of rosacea.

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Secondary features that may be present include burning/stinging, plaque, dry appearance, edema, ocular manifestations, peripheral location, and phymatous changes. Common patterns of features are grouped into 4 subtypes (erythematotelangiectatic, papulopustular, phymatous, and ocular) and 1 variation (granulomatous), described in Table I[2]. Differences in severity may occur within each subtype, and some patients may have features of more than one subtype simultaneously[2].

This standard classification has not yet been universally embraced by dermatologists, in part because it is perceived to be complex. However, this complexity reflects the attempt to precisely describe the numerous features of the rosacea syndrome and systematically organize them into definable subtypes. More time is needed to determine the validity and practical relevance of this classification in patient diagnosis and treatment. Nevertheless, careful assessment of each patient's disease features and determination of the relevant rosacea subtype(s) under the new classification can be useful in developing an effective individualized treatment plan for each patient, as discussed later in this article.

Table I. Characteristics of 4 rosacea subtypes and a variant[2]

Subtype	Characteristics
Erythematotelangiectatic	Flushing and persistent central facial erythema with or without telangiectasia.
Papulopustular	Persistent central facial erythema with transient, central facial papules or pustules or both.
Phymatous	Thickening skin, irregular surface nodularities, and enlargement. May occur on the nose, chin, forehead, cheeks, or ears.
Ocular	Foreign-body sensation in the eye, burning or stinging, dryness, itching, ocular photosensitivity, blurred vision, telangiectasia of the sclera or other parts of the eye, or periorbital edema.
Variant	
Granulomatous	Noninflammatory; hard; brown, yellow, or red cutaneous papules; or nodules of uniform size.

New Therapies for Rosacea

Several new agents have recently become available or are currently being explored for use in the treatment of rosacea. As shown in Table II, the Food and Drug Administration has approved a number of new or reformulated topical agents and light-based therapies for use in rosacea, while other agents remain in the investigational stage. The following section will review both newly approved therapies for rosacea and investigational agents that have shown early promise.

Oral Therapies

There have not been any major advances in systemic treatments for rosacea for several decades. The oral antibiotics (tetracycline, doxycycline, minocycline, erythromycin, and metronidazole) that are used off-label to treat rosacea, primarily the papulopustular subtype, have been available for the past 30 to 40 years[8,9]. While their efficacy is well established, the possible associated adverse events generally make long-term use undesirable. This is a serious problem given the chronicity of rosacea, which requires long-term maintenance therapy or repeated treatment of recurrences. Efforts to improve systemic therapy are currently focused on improving safety to permit extended use.

Early results suggest that a low, subantimicrobial dose of doxycycline may provide efficacy in rosacea with a reduced incidence of adverse events[10]. The tetracycline doxycycline hyclate is currently used as first- or second-tier therapy for rosacea at a daily dose of 100 - 200 mg[11-13]. Though it is generally well tolerated, known adverse events include skin rash, gastrointestinal distress, esophageal irritation, and (rarely) photosensitivity[8,11,13]. Tetracyclines, including doxycycline, have been discovered to have nonantimicrobial properties (i.e., inhibition of matrix-degrading metalloproteinases (MMPs)). At subantimicrobial doses, they have been shown to provide activity against chronic

Table II. New treatments recently FDA approved or under investigation for the treatment of rosacea

Topical Agents	Light-Based Therapies	Oral Antibiotics
New therapeutic class	**Intense pulsed light devices**	**Doxycycline hyclate**
Azelaic acid	**Various devices with outputs of 560-900 nm, spot sizes ranging from 4 8 mm to 10 50 mm, and maximum fluence ranging from 10 - 90 J/cm^2**	Subantimicrobial-dose 20 mg (Periostat®)
15% gel (Finacea™)	Aurora SR™ and SR/DS™	**Topical Agents**
Existing therapeutic classes	D-Light SR™	**Benzoyl peroxide**
Metronidazole	EsteLux™	5%/clindamycin 1% gel (BenzaClin®, Duac™)
Topical emulsion 0.75% (Rozex™)	Lux Y™ and Lux G™	**Tacrolimus**
Sulfacetamide 10%/sulfur 5%	IPL™ Quantum HR and SR	0.1% ointment (Protopic®)
Green tinted gel (Avar™ Green)	Multilight® HR	
Untinted gel and cleanser (Avar™)	OmniLight™ FPL	
Aqueous gel and cleanser in 10% urea vehicle (Rosula®)	Photoderm® VL/PL	
Alcohol-free emollient cream and foaming wash (Clenia™)	Platinum HR/SR	
pH neutral cleanser (Rosanil™)	Prolite™	
Combination cream with two sunscreens (Rosac®)	SpectrPulse®	
	Vasculight™ Elite, HR, SR, and VS	

periodontitis and acne without an effect on the bacterial microflora. Thus, efficacy is achieved with a low incidence of side effects and reduced risk of development of bacterial resistance[10].

Low-dose doxycycline hyclate (Periostat®) has recently shown promise in treatment of rosacea. An 8-week open-label study evaluated monotherapy with doxycycline 20 mg twice daily in patients with all stages of rosacea (N=50); most patients had received no prior treatment. At an average of 4 weeks, patients showed an 80% to 100% reduction in inflammatory lesions, a 50% decrease in erythema, and a decrease in the size and diameter of telangiectases. These outcomes are consistent with those reported for conventional doses of tetracyclines. No incidence of nausea, vomiting, headache, diarrhea, vaginitis, or photosensitivity was reported, even in patients who had previously reported such events while taking higher doses of doxycycline[10].

A phase 3 multicenter, double-blind, placebo-controlled trial (N=150) to evaluate the effectiveness of monotherapy with subantimicrobial-dose doxycycline (doxycycline hyclate 20 mg twice daily) for 4 months is currently being conducted. Results from this trial, expected in 2004, may help determine the future role of low-dose antibiotic therapy in the long-term treatment of rosacea.

Another possible new oral therapy for the management of rosacea is prophylactic use of baby aspirin. Migraine headaches are reported 2 to 3 times more frequently in rosacea patients, perhaps due to the vascular instability associated with both conditions[14,15]. Some neurologists recommend use of baby aspirin (81 mg enteric coated) as prophylaxis against migraine headaches. In Dr. Bikowski's personal experience over a 2-year period among approximately 100 patients who took 1 baby aspirin nightly, the majority reported a subjectively significant decrease in flushing and subsequent erythema after 1 to 3 months of treatment. However, to date there have been no controlled trials validating use of aspirin in rosacea.

Topical Agents

Over the past decade, improvements in the topical therapy arena have been limited to the development of new formulations (i.e., creams, lotions, gels, emulsions, cleansers) and different dose concentrations (e.g., 0.75% vs. 1%) of existing therapeutic agents, such as metronidazole and sulfacetamide 10%/sulfur 5%. This fine-tuning has contributed to improved delivery of the active agent into the skin, enhanced cosmetic acceptability of medications, and some reduction in skin irritation[16]. However, introduction of new topical agents that provide improved efficacy and/or tolerability can ultimately be expected to have a greater impact overall on patient well-being.

Azelaic acid gel

Azelaic acid is a naturally occurring dicarboxylic acid that has shown anti-inflammatory effects in vitro[17,18]. It has recently been developed as a polyacrylic-acid–based aqueous 15% gel

with several advantages over the 20% cream formulation, including improved drug release and absorption. The gel incorporates a higher percentage of micronized azelaic acid (25%) than the cream (3%). In vitro, 25.3% of the azelaic acid penetrated into viable skin when the gel was applied to hairless mouse skin in a Franz flow-through diffusion cell study, compared with only 3.4% of the cream[19,20]. The pH of the gel (approximately 4.8) is the optimum for maintaining formulation consistency and does not interfere with the skin acid mantle (pH approximately 5.5), in contrast to the more acidic cream (pH 3.3)[20].

Azelaic acid 15% gel (Finacea™) is the first new class of medication to be approved for the treatment of rosacea in more than 10 years. The effectiveness of azelaic acid 15% gel in reducing inflammatory papules and pustules and erythema has been demonstrated in 3 large phase 3 randomized, multicenter, double-blind trials: two pivotal 12-week vehicle-controlled studies (N=664)[21] which formed the basis of FDA approval, and a 15-week comparative study vs. metronidazole 0.75% gel (MetroGel®), currently the most widely used topical agent for rosacea (N=251)[22]. Treatment with azelaic acid gel resulted in significant percent reductions in inflammatory lesions, ranging from 51% to 73%. The percentage of patients whose erythema severity improved ranged from 44% to 56% in these 3 trials. In all trials, treatment with azelaic acid gel resulted in continuous improvement from visit to visit, and the differences vs. the comparator (vehicle or metronidazole gel) at the end of study were significant (P≤.02). At the end of each study, close to two thirds of patients (61% and 62% pivotal; 69% comparative) achieved "success" as defined by a new 7-point investigator's global assessment[21,22]. Figures 1A and 1B illustrate the symptom resolution in a patient with papulopustular rosacea after just 4 weeks of treatment with azelaic acid gel.

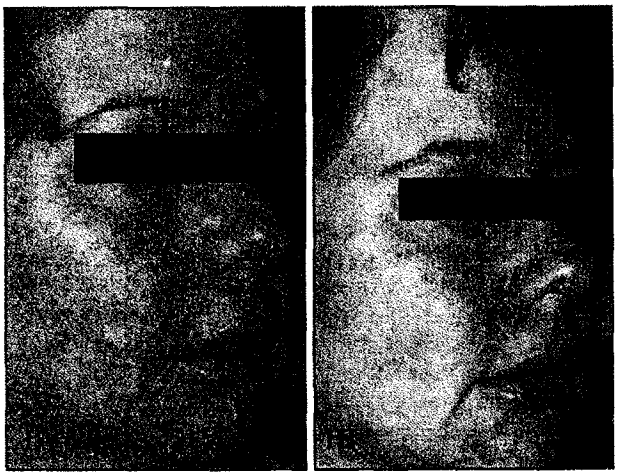

Figure 1A: Patient with papulopustular rosacea at baseline.
Figure 1B. Same patient after 4 weeks of twice-daily treatment with azelaic acid 15% gel.

In all trials, a higher incidence of patients treated with azelaic acid experienced adverse events, such as burning, stinging, tingling, or itching, which were mild and transient in the majority of patients[21,22]. Nevertheless, in clinical trials, around 90% of patients rated local tolerability good or acceptable despite minor irritation[21,22], and tolerability has not been reported to be a major patient concern in clinical use.

Based on its established efficacy against inflammatory lesions and erythema, demonstrated vs. both vehicle and metronidazole 0.75% gel, azelaic acid 15% gel is now considered a first-tier agent for the treatment of rosacea[23,24].

Metronidazole

Metronidazole has been used as a topical therapy for rosacea since its approval in 1988[25]. Numerous clinical trials have established its efficacy in reducing inflammatory papules and pustules and producing overall improvement, both as monotherapy and maintenance therapy[26,27]. Metronidazole is available in a variety of formulations (gel, lotion, cream) and strengths (0.75% and 1%), which have been shown to have equivalent efficacy[26,27]. In 2003, a water-based 0.75% topical emulsion (Rozex™), applied twice daily, was approved for topical treatment of papules and pustules of rosacea[28]. Although presented as a new product, its ingredients are identical to those in the metronidazole 0.75% topical cream (MetroCream®) formulation[28,29]. Because no clinical trial results have been reported, efficacy is expected to be similar to that of metronidazole cream. The most frequently reported adverse events (<3% of patients) with the emulsion are the same as with the cream: burning and stinging, erythema, skin irritation, pruritus, and worsening of rosacea[28,29].

Sulfacetamide 10%/Sulfur 5%

Sodium sulfacetamide 10%/sulfur 5% is a supplemental option for topical treatment of rosacea that is generally used in addition to, or after, oral or first-line topical therapies. It is used for the topical control of acne vulgaris, rosacea, and seborrheic dermatitis[30]. The efficacy of the sulfacetamide 10%/sulfur 5% combination in the treatment of rosacea was first established in the 1950s[30,31]. Since then, a plethora of different formulations of sulfacetamide/sulfur have become available, many in the last year alone. The first to be developed were lotions (currently marketed as Nicosyn™ and Sulfacet-R® tinted and tint-free), followed by topical suspensions and cleansers (Plexion®, Avar™, Rosula®, Rosanil™, Clenia™), creams (Plexion® SCT, Clenia™, Rosac®), and gel formulations (Avar Green™, Avar™, Rosula®).

Because of its pre-1962 regulatory status, the sulfacetamide 10%/sulfur 5% combination is known as a DESI (Drug Efficacy Study Implementation) drug[32]. As a result, information on the status of new agents and the drug approval process is not available through the FDA's Electronic Orange Book, which lists

only products approved based on safety and effectiveness[33]. Moreover, the core content of the prescribing information for each of these different formulations is identical and does not contain any supporting clinical data that would permit a critical or comparative analysis of the efficacy of these agents. The efficacy of the lotion and cleanser formulations has been established in a few small 8-week clinical studies (<100 patients each), which showed that treatment with sulfacetamide/sulfur reduced inflammatory lesion count, erythema severity, and overall rosacea severity[26]. Safety and tolerability are good, with rare reports of skin irritation, dryness, or redness.

Within the past year, 3 new water-based gels, an emollient cream, 3 cleansers, a foaming wash, and a cream with sunscreens, all containing sulfacetamide 10%/sulfur 5% as active ingredients, have become available for use in rosacea. Water-based gel formulations represent the latest technological advance in topical therapies, offering less irritation and better skin aesthetics[19]. A green-tinted sulfacetamide/sulfur gel (Avar Green™) may provide some patients with an additional immediate cosmetic benefit by masking the appearance of erythema. Green cosmetics have long been recognized as useful tools for camouflaging the redness of flushing and erythema[13]. Overlaying green onto red creates the perception of a more neutral flesh tone; however, the extent and duration of the perceptual effect in this sulfacetamide/sulfur gel have not been measured. Unlike cosmetics, the gel contains an active agent, so it should only be applied as directed, 1 to 3 times daily. A similar untinted gel and cleanser (Avar™) are also available[34].

Two other new formulations, an aqueous gel and a cleanser (Rosula®), are based in a 10% urea vehicle. The humectant properties of urea may help minimize irritation and dryness[35]. A new alcohol-free emollient cream and a foaming wash (Clenia™) also may have moisturizing effects that would be beneficial in patients with sensitive or dry skin[36]. An additional new cleanser formulation (Rosanil™) is fragrance free and pH neutral[37]. A small open-label study (N=31) of this sulfacetamide 10%/sulfur 5% cleanser, used in combination with twice-daily metronidazole 0.75% gel for 4 weeks, established its tolerability and showed a trend toward improvement in lesion count, erythema severity index, and overall rosacea severity[16].

Finally, a new sulfacetamide 10%/sulfur 5% cream combined with two non-PABA sunscreen agents (Rosac®) has also recently become available. The inclusion of avobenzone, a UVA filter, and octinoxate, a UVB filter, helps protect patients against sun exposure, which is a primary rosacea trigger factor[38]. In an investigator-blinded, randomized, parallel-group study (N=50) vs. metronidazole 0.75% cream (MetroCream®), 12 weeks of treatment with this sulfacetamide/sulfur/sunscreen cream resulted in a significantly greater improvement in the investigator's global severity rating (83% vs. 58% with metronidazole cream). In addition, significant differences in percent reduction in inflammatory lesions (82% vs. 68%) and percent of patients with improved erythema (63% vs. 42%) were observed with sulfacetamide/sulfur/sunscreen cream compared with metronidazole cream, respectively[30].

While each of these formulations is unique, the active ingredients are identical to each other and to existing sulfacetamide/sulfur agents. With the exception of the combined sunscreen formulation, no new clinical data is available for these new products, thus efficacy can be expected to be similar to that of other sulfacetamide/sulfur products currently in use. Clinical experience will remain paramount in distinguishing between these products and determining how they can best be used to benefit patients.

Investigational Treatments

The following topical agents are not yet approved for use in rosacea but have shown some activity against it in exploratory investigations. Larger controlled trials will be needed to confirm their efficacy and safety in rosacea patients.

Benzoyl peroxide/clindamycin gel

Topical clindamycin 1% has shown efficacy in rosacea38 and is currently available as both a lotion (Cleocin T®) and a gel (Clindagel®). It is considered a second-tier treatment option[23]. Combination gels containing clindamycin 1% and benzoyl peroxide (BP) 5% (BenzaClin®, Duac™) are an approved treatment for acne vulgaris[39,40]. A small exploratory trial has investigated the utility of BP/clindamycin, applied once daily, for the treatment of moderate rosacea. In a 12-week, randomized, double-blind, multicenter, placebo-controlled trial (N=53), a >70% reduction in inflammatory lesions was achieved with BP/clindamycin (P≤.02 vs. placebo) by week 6, and was maintained through week 12. Reductions in erythema, flushing and blushing, and overall severity of rosacea were also observed in patients treated with BP/clindamycin (P≤.001). Treatment with BP/clindamycin resulted in a 30% improvement in overall rosacea severity vs. 10% with placebo[24,41].

Tacrolimus ointment and pimecrolimus cream

Tacrolimus and pimecrolimus are nonsteroidal immunomodulators that act by calcineurin inhibition. They prevent inflammation primarily by inhibiting cytokine production and blocking T-cell activation in a manner similar to that of cyclosporine[42-45]. Tacrolimus 0.1% ointment (Protopic®) and pimecrolimus 1% cream (Elidel®) have recently been approved for the treatment of atopic dermatitis when conventional therapy is inadvisable[44,45]. Because of its anti-inflammatory properties, tacrolimus is currently being evaluated for use in a variety of other inflammatory skin conditions, including rosacea[43].

Several case studies have suggested that tacrolimus 0.075% or

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