Rosacea: An Update on Medical Therapies

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Introduction

Rosacea is a common, chronic cutaneous condition that affects the face. Several topical medications are currently approved for the treatment of rosacea, including azelaic acid and metronidazole. Systemic therapy utilizing a sub-antimicrobial dose of doxycycline is also effective in treating rosacea. Identification of subtypes can help guide treatment strategies. Psychosocial implications of rosacea must be considered and conservative management, such as skin care, must form an important part of the overall care. Recently, new insights into the pathophysiology of rosacea have led to the emergence of etiologically oriented treatments, including the newly approved brimonidine gel 0.33% (Onreltea™).

Background

- Rosacea is a common chronic cutaneous condition that primarily affects the central facial area, including the cheeks, nose, eyes, chin and forehead.\(^1\)
- Primary cutaneous manifestations include sensitive skin, flushing, persistent erythema, papules, pustules and telangiectases.
- Although symptoms may wax and wane in the short-term, rosacea is slowly progressive in the long-term for many patients.\(^2\)
- The National Rosacea Society has classified rosacea into four main subtypes: \(^3\)
  1. Erythematotelangiectatic
  2. Papulopustular
  3. Phymatous
  4. Ocular
- Progression from one subtype to another is possible.\(^4\) Proper identification of subtypes may help guide therapeutic strategies.
- Rosacea affects up to 10% of the general population and the onset is typically between the ages of 30 and 50 years.\(^5\)
- It is especially common in light-skinned individuals of northern European descent, with women more frequently affected.\(^5,6\) However, men are more prone to develop thickening and distorted phymatous skin changes, especially of the nose.
- While rosacea was considered rare in people of colour, a recent increase in case reports documenting rosacea in patients with Fitzpatrick Skin Types IV-VI, suggests that it is more common in darker skinned individuals than previously thought, and may have been underrecognized and unreported in the dermatology literature.\(^7,8\)
- Rosacea pathophysiology is multifactorial and currently not fully understood. Factors proposed to play a role include vascular abnormalities, gastrointestinal disorders, matrix...
degeneration, pilosebaceous gland abnormalities, microbial activity, and altered innate immune response.

- Rosacea can create psychosocial burdens, such as embarrassment, anxiety and low self-esteem, and adversely affect quality-of-life, which should be taken into consideration when treating these patients. Conservative measures, such as trigger avoidance, proper skin care, camouflaging cosmetics, and photo-protection should also be incorporated into the management plan.

**Conventional Therapies**

**Topical Metronidazole**
- Metronidazole (Noritate® 1% Cream, Dermik; Metrogel 1%, Metrocream™ 0.75% Cream, Metrolotion® 0.75% Lotion, Metrogel® 0.75% gel), first demonstrated efficacy against rosacea in the 1980s.
- Despite being an antibacterial and antiprotozoal agent, metronidazole confers its therapeutic efficacy mostly through its anti-inflammatory and antioxidant effects.
- Multiple trials have demonstrated that topical metronidazole significantly decreases the number of inflammatory lesions and reduces erythema compared to placebo; is generally well tolerated; has a low incidence of adverse effects; and is effective in maintaining remission.
- Importantly, different formulations of metronidazole have demonstrated similar efficacy, regardless of vehicle type (cream, gel, or lotion) or concentration (0.75% or 1%).
- Once- and twice-daily applications have similar efficacy.
- Metronidazole 1% has demonstrated less cumulative potential for irritation over a 21-day period, (similar to that of white petrolatum) compared with metronidazole gel 0.75%.
- When combined with sunscreen SPF 15, metronidazole may reduce development of facial telangiectasia.
- Topical metronidazole is a pregnancy category B medication.

**Topical Azelaic Acid**
- Azelaic acid (Finacea®) is a naturally occurring dicarboxylic acid approved in the last decade for the treatment of mild to moderate rosacea.
- Mostly applied as a 15% gel or a 20% cream, azelaic acid has anti-inflammatory, antikeratinizing, and antibacterial effects.
- Multiple trials have demonstrated that azelaic acid is more effective than placebo at reducing the number of inflammatory lesions and degree of erythema. The pooled rates of patients showing marked improvements with azelaic acid treatment were 70-80%, compared to 50-55% with placebo.
- Azelaic acid also has a relatively low incidence of adverse effects, with burning, stinging and irritation being the most commonly reported. However, data from Colon et al, show that azelaic acid gel 15% caused significantly more irritation than white petrolatum when administered over a 21-day period, as well as both concentrations of metronidazole (p<.0001 for all comparisons).
- Although the conventional regimen is twice-daily application, once-daily dosing has been found to be equally effective.
- Further studies are needed to support the use of azelaic acid as a maintenance therapy.
- It is currently a pregnancy B category medication.

**Tetracycline**
- While not indicated for the treatment of rosacea, oral antibiotics have been recognized for the past 50 years as an effective treatment and are thought to exert their therapeutic effects primarily via anti-inflammatory rather than antibacterial mechanisms.
- Because the role of micro-organisms in rosacea pathogenesis remains unclear, the use of antibiotics at standard doses is not an ideal approach.
- However, the tetracycline-family of antibiotics is effective in treating ocular rosacea, which typically affects greater than 50% of patients with rosacea.
- Tetracyclines are the most frequently used class of antibiotics with greatest efficacy against inflammatory papules and pustules.
- Tetracyclines are contraindicated in pregnant women.
- Second-generation tetracyclines, including minocycline and in particular doxycycline, are especially safe and effective oral therapies for rosacea.
- Unlike the parent, second generation tetracyclines have greater bioavailability, rapid onset of action, and can be taken with food, which minimizes gastrointestinal side effects.
- Second-generation tetracyclines require once-daily dosage, which may improve compliance.
- Most importantly, they are effective at a sub-antimicrobial dose, which avoids disruption of the endogenous flora and, of global importance, the propagation of antibacterial resistance.
- Recently, two phase 3, multicenter, randomized, double-blind, placebo-controlled clinical trials demonstrated that a daily sub-antimicrobial dose of 40 mg doxycycline (Apprilon™), administered to patients with moderate to severe rosacea, significantly reduced total inflammatory papule and pustule counts compared with placebo after 16-weeks treatment, with significant improvements evident at 3 weeks.
- Prevalence of adverse effects was low and only marginally higher than placebo, with nasopharyngitis (4.8%), diarrhea (4.4%) and headaches (4.4%) being the most commonly reported.
- No cases of photosensitivity or vaginal candidiasis occurred.
- A separate study demonstrated that the effectiveness of 40 mg doxycycline is comparable to that of 100 mg doxycycline in rosacea but with a lower incidence of gastrointestinal side effects.

**New Therapies**

**Brimonidine**
- Diffuse facial erythema has long posed an unmet need in rosacea management.
- One contributing factor is abnormal cutaneous vasomotor responses, which leads to persistently enlarged facial blood vessels. These blood vessels remain responsive to vasoactive stimuli, hence the growing interest in α2-
adrenergic receptor agonists as a possible therapeutic option.\textsuperscript{36}

- Brimonidine 0.33\% gel (Mirvaso\textsuperscript{TM}), approved by FDA in August 2013, is the latest addition to the therapeutic armamentarium and the first topical agent approved for the treatment of facial erythema of rosacea. This formulation was recently approved by Health Canada with the trade name Onreltea\textsuperscript{®}, for the topical treatment of facial erythema of rosacea in adults 18 years of age or older.\textsuperscript{11} (*Note-the literature refers to both brimonidine gel 0.33\% and brimonidine tartrate gel 0.5\%. This is the same product and the terms are interchangeable.)

- Brimonidine is a highly selective \(\alpha_2\)-adrenergic receptor agonist with potent vasoconstrictive activity and is also found in prescription eye drops for the treatment of glaucoma.\textsuperscript{37}

- In two phase 3 randomized, double-blind pivotal trials, topical brimonidine tartrate gel 0.5\% once daily was significantly more effective than vehicle over a 4-week treatment period.\textsuperscript{38} In the two trials, approximately 24.82\% of the patients using brimonidine tartrate gel 0.5\% versus (vs.) 9.76\%; \(p<0.05\) on day 29 were assessed to have at least a two-grade improvement by both clinicians and patients over 12 hours after drug application, with peak improvements observed at 3 and 6 hours (Fig. 1 and 2).

- Noticeable improvement (one-grade Clinician’s Erythema Assessment and 5 point Patient Self Assessment Scale) was observed (28.2\% vs. 5.9\%; \(p<0.01\) as early as 30 minutes after the first application on day one.

- Adverse events were mildly elevated in the treatment group but were largely cutaneous, transient and mild, with the most commonly reported being worsening of erythema (5.1\%), pruritus (5.0\%), skin irritation (1.2\%), and rosacea (1.1\%).

- There was no evidence of tachyphylaxis, rebound, or aggravation of telangiectasia or inflammatory lesions.

- Data from a 12-month, multi-center, open-label study also show no incidence of tachyphylaxis, with efficacy maintained over the long-term.\textsuperscript{39}

Other Therapies

- Topical sodium sulfacetamide 10\% with sulfur 5\% has been used for over 50 years for its clinical efficacy and safety in the treatment of rosacea, although its mechanism of action is not well understood.

- In an 8-week study, sulfacetamide 10\% with sulfur 5\% has been shown to significantly reduce inflammatory lesions (78\% vs. 36\%; \(p<0.001\) and facial erythema (83\% vs. 31\%; \(p<0.001\) compared to vehicle.\textsuperscript{4,40} Studies evaluating this therapy, however, are limited and generally of poor quality.\textsuperscript{40}

- Laser and light therapies have been used successfully for many years to treat the vascular manifestations of rosacea.

- In a randomized, controlled, single-blind, split-face trial, both pulsed dye laser and intense pulse light were found to be effective, with similar efficacy in reducing erythema and telangiectasia in patients with erythematotelangiectatic rosacea.\textsuperscript{41}

Conclusion

Therapeutic decision-making in the treatment of rosacea should be guided by high-level evidence, where available, and will depend on subtype, severity, patient expectations, tolerance, budget and previous therapy used. Topical azelaic acid and metronidazole are considered safe and efficacious first-line therapies. A sub-antimicrobial dose of doxycycline is the best research-supported oral therapeutic indicated for the treatment of rosacea and provides a safe and convenient option.
for patients who prefer oral to topical therapy. Light and laser-based therapies play a major clinical role in the treatment of the telangiectatic component. The promising novel therapy, brimonidine, fills a much-needed niche in the targeted treatment of facial diffuse erythema of rosacea.

References
Clinical Management of Recurrent Herpes Labialis

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Introduction

Herpes simplex virus (HSV) is responsible for an infection around the lips (herpes labialis) that often occurs with a longer primary infection and then may result in shorter recurrences (cold sores, fever blisters). Herpes simplex infection is ubiquitous in the adult population with various studies documenting between 60-90% of tested individuals having previous infections. Currently available treatments include prescription and non-prescription drugs in topical and oral formulations, with antiviral medications representing a mainstay of treatment. They are reviewed below, as are data from a clinical trial of a new formulation of topical 5% acyclovir with 1% hydrocortisone cream (Xerese®).

Background

• Most herpes labialis lesions are caused by herpes simplex type 1 (HSV-1). Genital herpes simplex is predominantly herpes simplex type 2 virus (HSV-2).
• With an increase in oral sex, there are more cases (although still a minority) of herpes labialis associated with type 2 infections.
• Primary HSV infection in children or young adults may cause severe stomatitis and pharyngitis with an erosive, painful infection of the buccal mucosa and gums.
• Primary infections may be associated with pain on swallowing and lymphadenopathy.
• In adults, the primary infection may be limited to a pharyngitis without involvement of the mouth (gingival- stomatitis).
• Some primary infections are completely asymptomatic.
• Viral shedding and potential spread of infection is most common with an open lesion.
• After the primary infection, the virus remains latent in the sensory nerve (Trigeminal) ganglion of the facial nerve for life. It may re-activate at a later date, in a non-primary episode, with a clinical course that is often less severe than a primary episode but more severe than a typical recurrence.
• Asymptomatic viral shedding can occur sporadically between acute episodes and result in spread of the infection.
• Recurrent infections follow a shorter time period and have a number of identifiable stages, specifically:
  1. Prodrome: tingling, itching, burning or local pain may occur for a few hours up to a couple of days prior to the development of local erythema.
  2. Day 1 of the eruption is often associated with virus replication at the end of the nerve and in the epithelial cells resulting in local erythema and swelling.
  3. Days 2-3 (or sooner) results in the appearance of tender papules and subsequent vesicles usually around the lips but the lesions may appear on the nose, chin or cheeks.
  4. Day 4 or sooner, a painful ulcer may develop from ruptured vesicles that may coalesce into a larger single ulcer with the characteristic herpetiform edges that have a semi-circular peripheral appearance similar to the outline of a cluster of grapes. The serous or serosanguinous discharge is loaded with viral particles and represents the most contagious stage of the cold sore. Submental lymphadenopathy may be present but is less severe than signs associated with a primary infection. Secondary bacterial infection with staphylococcus or streptococcus may result in a pustular element to the discharging fluid.
  5. Days 5-8 is the crusting stage (serosanguinous, occasionally pustular) which forms from the dried exudate.
  6. The healing stage can take from day 9 to day 14 but is variable. It may be shorter with aborted recurrent episodes or with early treatment at the prodrome or early lesion stage.

Diagnosis

• The diagnosis of herpes labialis is often recognized by the clinical appearance alone.
• If a lesion is atypical, laboratory investigations can be ordered that will identify HSV-1, HSV-2, or return a negative result (more common from late lesion samples).

Patient Impact

A recent survey of 231 patients (age >18 years) with recurrent herpes labialis (outbreaks at least once a year) revealed that cold sores had a severe negative influence on social life/self-image in 55.5% of survey respondents. Additional findings include:
• The most troublesome aspects of the cold sores are the blister/ulcer and the subsequent crust formation.
• The duration of the cold sores can be prolonged and more significant than acknowledged by many clinicians.
• The majority of infected individuals (65.9%) preferred topical treatment, either over-the-counter or prescription treatment for cold sore recurrences.
• 77.2% preferred a topical preparation for the first sign of an outbreak (46.2% prescription, 31% non-prescription) and 9.6% would prefer not to prevent or treat outbreaks. Oral prophylaxis was preferred by 19.8% with a topical agent for a breakthrough.

Treatment of Recurrent Herpes Simplex Labialis

Topical Prescription Drugs

A recent, multicenter, randomized, double-blind study identified the combination of 5% acyclovir with 1% hydrocortisone cream (Xerese®) as effective and well tolerated in the control of herpes simplex labialis recurrences in adults.1

• Topical acyclovir (Zovirax®) is a nucleoside antiviral agent that targets the viral replication stage.2 The 1% hydrocortisone component is anti-inflammatory, designed to decrease the host response time post viral replication.2
• The study compared a new base of 5% acyclovir with 1% hydrocortisone cream to 5% acyclovir base and the Xerese® vehicle base cream. The study included 1,443 treated subjects with 601 receiving combination 5% acyclovir / 1% hydrocortisone cream, 610 receiving topical acyclovir cream, and 232 placebo cream for a randomization ratio of 2.7/2.7 to 1.
• The number of patients not progressing to the ulcerative stage compared to non-ulcerative recurrences was 42% for the acyclovir combined with 1% hydrocortisone (Fig. 1) compared to 35% for acyclovir cream alone (p=0.14) and 20% for Xerese® vehicle alone (p=0.001). This is the first study to demonstrate effectiveness of topical acyclovir cream compared to the vehicle alone.
• The enhanced effect was likely due to the reformulation with the partial replacement of propylene glycol with isopropyl myristate that enhances stratum corneum penetration of the topical acyclovir.
• The addition of the anti-inflammatory effect of topical 1% hydrocortisone further enhanced the effectiveness of the topical acyclovir in the new cream formulation.

![Figure 1. Similar efficacy between Xerese® and Valtrex® in preventing ulcerative lesions](image)

Similarly reduced cold sore ulceration and duration of ulcerative lesions1,4 by Hull CM, Brunion S. The Role of topical 5% Acyclovir and 1% hydrocortisone Cream (Xerese) in the Treatment of Recurrent Herpes Simplex Labialis: Postgraduate Medicine. Vol 122, June 5, Sept 2010. ISSN = 0032-5481.

£ Adapted from Spruance et al. High-Dose, Short Duration Early Valacyclovir Therapy for Episodic Treatment of Cold Sores: Results from Two Randomized, Placebo-controlled, multicenter studies.

The cumulative lesion area in the study was calculated from the area of the ulcerative lesions that were added from daily measurements. The combination of 5% acyclovir with 1% hydrocortisone had a cumulative lesion area that was 50% smaller than the placebo cream cumulative area (p<0.0001), and the 5% acyclovir area was 25% smaller than the placebo cream cumulative area.

• Healing of lesions with the combination cream occurred in 3 vs. 4 days for acyclovir cream and 5 days for the placebo cream.
• The average lesion tenderness duration with the combination cream was 5 days, similar to acyclovir cream but less than the 6 day average for placebo cream (p=0.019). Positive cultures for herpes simplex were no higher with the combination cream (22%) compared to acyclovir cream alone (24%) and less than the placebo cream (40%).
• Overall adverse event rates were similar in all 3 groups.
• The combination cream is applied 5 times per day for 5 days.
• These results can be compared favourably to a previous study by Shaw et al, using an original vehicle formulation of topical acyclovir.7 This older formulation of topical acyclovir in the relatively small number of subjects failed to demonstrate benefit in 45 patients with 72 recurrences.

Spruance et al, combined the results of two randomized clinical trials (RCTs) comparing the original topical 5% acyclovir cream with placebo cream in 1,385 subjects, and found a reduced time to healing with the 5% acyclovir preparation, from 5 to 4.4 days.8

Topical Non-Prescription Formulations

• Topical docosanol (Abreva®) is a saturated fatty alcohol proposed to be effective in preventing the HSV envelope from attaching to the host cell.
• Sacks et al, published results of an RCT with 737 patients comparing the 10% docosanol cream to a placebo (polyethylene glycol) in the prodromal stage.9
• Treatment with docosanol cream significantly (p=0.002) shortened the duration of pain, itching, tingling or burning and reduced the time to complete healing (p=0.002).9
• Docosanol cream has a low risk of drug resistance.
• Symptomatic relief may be obtained by preparations with local anesthetic effects including Blistex® with menthol, phenol and camphor and zilactin with benzoyl alcohol.10
• Propolis extract from honey is the active component in ColdSore-FX® with in vitro anti-inflammatory and antimicrobial properties.10

Oral Prescription and Non-Prescription Drugs

• Effective oral antiviral medications that can speed the healing of labial herpes simplex recurrences include acyclovir and penciclovir.
• Spruance et al, conducted an RCT of 114 subjects with recurrent herpes labialis treated with oral acyclovir 400 mg 5 times a day for 5 days compared to 60 patients given a similar course of placebo treatment. The lesions treated with acyclovir were less painful and healed faster compared to placebo.11
• Valacyclovir (Valtrex®) is the prodrug of acyclovir. It increases gastrointestinal absorption of the antiviral agent. Spruance et al, conducted a high-dose, short duration, early
valacyclovir treatment RCT for recurrent episodes of labial cold sores vs. placebo. The dose of valacyclovir was either 2 grams twice daily for 1 day or with the addition of 1 gm twice daily on day 2. There were more aborted episodes with both of these treatment regimens compared with placebo, but the episode duration was reduced by a half to one day.

- Famciclovir, (Famvir®) the prodrug of penciclovir, increases the gastrointestinal absorption of this antiviral agent. An RCT conducted with high dose famciclovir (750 mg twice daily or 1500 mg in a single dose) vs. placebo showed that recurrences healed in both active groups in 4 vs. 6 days with placebo.

- The newer, high dose, short treatment duration studies have shown better therapeutic efficacy compared to the traditional treatment of lower doses over 5-7 days.

- One non-prescription drug, oral lysine, is available in most health food stores. This medication has been popular with patients for the treatment or prevention of herpes labialis based on in vitro studies but the evidence supporting this treatment in humans is inconclusive.

**Prevention**

- A study by Rooney et al, utilizing an experimental system of ultraviolet light to induce reactivation of herpes labialis lesions did not produce any lesions in 35 patients using sunscreen but reactivated a herpes lesion in 27 of 38 patients (71%) utilizing the placebo sunscreen.

- Continuous prophylaxis is often considered for individuals with 6 or more herpes lesions per year. Twenty patients completed a randomized, 4-month crossover trial with oral acyclovir 400 mg twice daily or placebo. Placebo treatment was associated with 1.8 reactivation episodes per subject while the continuous prophylaxis had 0.85 reactivation episodes.

- Similar continuous prophylaxis has also been proposed for valacyclovir at a dose of 500 mg or 100 mg p/day or famciclovir 250 mg or 500 mg daily.

**Conclusion**

Because oral antivirals have a narrow therapeutic window, they should be initiated at the prodromal stage. However, if the antiviral medication is taken after the prodromal stage, efficacy is decreased significantly. The oral medication has no effect on the inflammatory component of a cold sore. A way to optimize treatment is to offer patients two options, i.e. oral therapy and the topical treatment that contains acyclovir 5% and hydrocortisone 1% (Xerese®). The combination would address not only the viral replication but the inflammatory response. This strategy could potentially optimize patient outcomes.

**References**
