Rosacea: An Update on Medical Therapies

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Abstract
Rosacea is a common, chronic cutaneous condition that affects the face. Two topicals and one oral medication are currently approved for the treatment of rosacea, including azelaic acid, metronidazole, and sub-antimicrobial dose of doxycycline. Identification of subtypes can help guide treatment strategies. It is essential for psychosocial implications of rosacea to be considered and conservative management, such as nonpharmacologic routine 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. Ivermectin, an acaricidal agent that has been shown to be effective against rosacea refractory to other therapies, is currently in Phase 3 trials. Brimonidine, which was US FDA approved last year and recently sanctioned by Health Canada, has filled an essential therapeutic void in the targeted treatment of diffuse facial erythema.

Key words: alpha-2 adrenergic receptor agonists, anti-bacterial agents, antiparasitic agent, erythema, inflammation, rosacea, telangiectasia

Introduction
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: erythematotelangiectatic, papulopustular, phymatous, and ocular.³ 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 onset is typically between the ages of 30 and 50 years.³ It is especially common in light-skinned individuals of Northern European descent,³ with women more frequently affected,¹ but men are more prone to develop thickening and distorting phymatous skin changes, especially of the nose. Although infrequent, some cases have been diagnosed in darker skin types; however, under-diagnosis and low reported incidence may be attributable to sampling bias and decreased visibility of clinical signs (e.g., erythema and telangiectasias).⁷

The pathophysiology is multifactorial and currently not fully understood. Multiple factors have been proposed to play a role, including vascular abnormalities, gastrointestinal disorders, matrix degeneration, pilosebaceous gland abnormalities, microbial activity, and altered innate immune response.⁵⁶ A new understanding of rosacea pathogenesis is emerging and alongside it the development of novel agents that target specific pathogenic factors and the symptoms they induce.

Rosacea can create psychosocial burdens, such as embarrassment, anxiety, and low self-esteem that adversely affect quality of life. These negative impacts should be taken into consideration when treating rosacea patients.¹⁰¹¹ Conservative measures, such as trigger avoidance, proper skin care, and the use of camouflage cosmetics and photoprotection should also be incorporated in the management plan.¹²

Conventional Therapies

Topical Metronidazole
Metronidazole was first shown to be an effective treatment against rosacea in the 1980s.¹³ Despite being an antibacterial and antiprotozoal agent, metronidazole’s therapeutic benefits in rosacea are mostly derived through its anti-inflammatory and antioxidant effects.¹⁴ 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.¹⁵¹⁶ Importantly, different formulations of metronidazole have been demonstrated to have similar efficacy, regardless of vehicle type (cream, gel, or lotion) or concentration (0.75% or 1%).¹⁹²¹ Once-daily dosing was also confirmed to be similarly effective as twice-daily application.¹⁹²² In addition, when combined with a sun protection
factor 15 sunscreen, metronidazole may reduce the development of facial telangiectasia. Of note, topical metronidazole is a pregnancy category B medication.

**Topical Azelaic Acid**

Azelaic acid 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 can attribute its efficacy to anti-inflammatory, anti-keratinizing, 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 with 50-55% in the placebo group. Azelaic acid also has a relatively low incidence of adverse effects, with burning, stinging, and irritation being the most commonly reported. The incidence of side effects is greater with azelaic acid compared with metronidazole, but these effects are generally mild and transient. Although the conventional regimen is twice-daily application of azelaic acid, 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 listed as a pregnancy B category medication.

**Tetracyclines**

Off-label use of oral antibiotics has been recognized for more than 50 years as an effective treatment for rosacea. Therapeutic benefits of tetracyclines in rosacea are primarily a consequence of their anti-inflammatory rather than antibacterial mechanisms, as there is insufficient evidence to support a bacterial infection in disease pathogenesis. Tetracline-family antibiotics should particularly be considered in the presence of ocular rosacea, which typically affects greater than 50% of patients with rosacea. Tetracyclines, which are contraindicated in pregnant women, are the most frequently used class of antibiotics and are most effective against inflammatory papules and pustules.

Second-generation tetracyclines, including minocycline and in particular doxycycline, are especially safe and effective oral therapies for rosacea. Unlike the parent tetracycline, they have greater bioavailability, rapid onset of action, and can be taken with food, which minimizes gastrointestinal side effects. Additionally, second-generation tetracyclines only require once-daily dosing, which may improve compliance. Most importantly, they are effective at a sub-antimicrobial dose, thereby avoiding disruption of the endogenous flora and, of global importance, the propagation of antibiotic resistance.

Recently, two Phase 3, multicenter, randomized, double-blinded, placebo-controlled clinical trials demonstrated that a sub-antimicrobial dose of 40 mg doxycycline administered daily to patients with moderate to severe rosacea significantly reduced total inflammatory papule and pustule counts compared with placebo after 16 weeks of treatment, with significant improvements observed 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. There were no cases of photosensitivity or vaginal candidiasis. A separate study demonstrated that the efficacy of 40 mg doxycycline is comparable to that of 100 mg doxycycline in rosacea. Sub-

**New and Emerging Therapies**

**Topical Ivermectin**

Several topical acaricidal agents (permethrin 5%, crotamiton 10%, and ivermectin 1%) have been studied for the treatment of rosacea, all of which primarily target Demodex folliculorum and Demodex brevis mites. The potential etiological role of these mites in rosacea has been debated for many years. There is renewed interest in Demodex mites due to recent studies that demonstrated antigenic proteins produced by a Demodex-isolated bacterium (Bacillus oleronius) may aggravate the inflammatory responses in papulopustular and ocular rosacea, as well as in erythematotelangiectatic rosacea. This pathogenic scenario implicating the bacterium rather than the Demodex mites themselves may explain the efficacy of antibacterial therapies in rosacea.

Numerous case reports have been published on the successful treatment of rosacea with topical acaricidal agents refractory to other therapies, however, data from controlled, randomized trials are lacking. Phase 3 randomized clinical trials studying the impact of topical ivermectin 1% cream in rosacea are underway, which compare its efficacy and safety with metronidazole 0.75% cream and azelaic acid 15% gel. Results are expected to be evaluated in the near future.

**Topical Brimonidine and Oxymetazoline**

Diffuse and persistent facial erythema has long been a clinical challenge in rosacea therapy. One contributing factor to diffuse facial erythema is abnormal cutaneous vasomotor responses, which leads to enlarged superficial facial blood vessels. Importantly, however, these blood vessels remain responsive to vasoactive stimuli, hence, the growing interest in alpha (α)-2 adrenergic receptor agonists as a therapeutic option to manage the nontransient erythema.

Brimonidine tartrate 0.33% gel, approved by the US FDA in August 2013 and by Health Canada in February 2014, is the latest addition to the treatment armamentarium and the first topical agent approved for the treatment of facial erythema of rosacea. Brimonidine (initially available in prescription eye drops for the treatment of glaucoma) is a highly selective α-2 adrenergic receptor agonist with potent vasoconstrictive activity.

In two Phase 3 randomized, double-blind pivotal trials, topical brimonidine tartrate (BT) gel 0.5% once-daily was found to be significantly more effective than vehicle over a 4 week treatment period. In the two trials, approximately 24.82% of the patients using BT gel 0.5% (vs. 9.76%; p<0.05) were assessed on...
day 29 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. Noticeable improvement (one-grade based on Clinician’s Erythema Assessment and Patient’s Self-Assessment) was observed (28.2% vs. 5.9%; p<0.01) as early as 30 minutes after the first application on day 1. Adverse events were mildly elevated in the active treatment group, but events were mostly skin-related, transient, and mild, with the most commonly reported being worsening of erythema (5.1%), pruritus (5.0%), skin irritation (1.2%), and worsening of rosacea (1.1%). There was no evidence of tachyphylaxis, rebound, or aggravation of telangiectasia or inflammatory lesions. Additionally, recently published data from a 12-month, multicenter, open-label study reported sustained efficacy with no incidence of tachyphylaxis in the long-term treatment of moderate to severe erythema of rosacea. Phase 2 clinical trial for another promising α-adrenergic receptor agonist, called oxymetazoline, has recently been completed. Results should be available in the near future.

Other Therapies

Topical sodium sulfacetamide 10% with sulfur 5% has been used for more than 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. However, studies evaluating this therapy are limited and generally of poor quality. Oral isotretinoin can be used off-label for the treatment of more severe or persistent cases of papulopustular rosacea and may help slow or halt the progression of rhinophyma. In a large scale, randomized, double-blind, 12-week study comparing different doses of isotretinoin to doxycycline and placebo in the treatment of rosacea, isotretinoin 0.3 mg/kg demonstrated non-inferiority to doxycycline (p=0.00001) and was well tolerated. However, isotretinoin should only be prescribed with close monitoring and, particularly in women with childbearing potential, an appropriate contraception strategy is essential due to its teratogenic potential. 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 modalities were found to be effective, with similar efficacy, in reducing erythema and telangiectasia in patients with erythematotelangiectatic rosacea.

In a double-blind, randomized, vehicle-controlled, 12-week clinical trial, off-label use of topical benzoyl peroxide 5% with clindamycin 1% once-daily was shown to be effective in reducing papule and pustule count in patients with rosacea compared to vehicle alone (71.3% vs. 19.3%; p=0.0056). Adverse events were only mildly elevated in the treatment group, with localized burning and itching being the most commonly reported.

Pimecrolimus 1% cream was demonstrated in an open-labeled, uncontrolled, 4-week trial to be effective and well tolerated in the treatment of rosacea. Adverse events were transient and mild, which included local burning, itching, dryness, and stinging.

Conclusion

There are numerous treatment options available for rosacea, however, only a handful of agents are substantiated with quality research. If available, therapeutic decision-making should be guided by high-level evidence and patient-specific factors, such as rosacea subtype, severity, treatment expectations, tolerance, cost, and previous response to therapy. Topical azelaic acid and metronidazole are considered safe and efficacious first-line therapies. Sub-antimicrobial dose of doxycycline is the best research-supported oral therapeutic option and can be used to treat moderate to severe forms of papulopustular or ocular rosacea, or in patients who may be more adherent on a systemic regimen. Low-dose isotretinoin or surgical interventions may be indicated for the phymatous type. Light and laser-based therapies can play a major clinical role in the treatment of the telangiectatic component. The novel therapy, brimonidine, provides targeted treatment of facial diffuse erythema of rosacea. A comprehensive treatment plan must also incorporate non-drug strategies aimed at quality of life improvements and include trigger avoidance, proper daily skin care, camouflageing and photoprotection. Further research is needed on the effectiveness of combination treatments, isotretinoin, sulfacetamide, light-based options, and newly emergent agents compared with conventional therapies.

References


29. Colon LE, Johnson LA, Gottschalk RW. Cumulative irritation potential among metronidazole gel 1%, metronidazole gel 0.75%, and azelaic acid gel 15%. Cutis. 2007 Apr;79(4):317-21.


Recent Approval of Xerese in Canada: 5% Acyclovir and 1% Hydrocortisone Topical Cream in the Treatment of Herpes Labialis

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ABSTRACT
Herpes labialis is a frequently occurring viral infection of the lips and oral mucosa. Recurring lesions are induced by viral reactivation and replication, but the symptoms leading to morbidity, such as pain and inflammation, are immune-mediated. The introduction of 5% acyclovir/1% hydrocortisone in a topical cream (Xerese™) represents a therapeutic strategy directed at both of these pathogenic processes. Applied at the onset of prodromal symptoms, this combination treatment has a good safety profile and is more effective in reducing healing time than antiviral or anti-inflammatory agents alone. Although it was US FDA-approved for herpes labialis in 2009, Xerese™ has only recently been approved for use in Canada in October 2013. Herein, we review the basic science and clinical studies that support the efficacy of this topical combination acyclovir-hydrocortisone product in treating herpes labialis and examine its safety profile, as well as touch upon other therapies that have been shown to be effective in treating this common viral condition.

Key words: cold sores, herpes labialis, Xerese, viral infection, Canada, drug approval

Introduction
Herpes labialis (colloquially known as “cold sores”) is a common viral infection characterized by vesicular lesions of the lips and oral mucosa. It is estimated to affect 1 in 5 Canadians annually and is associated with a negative stigma that can lead to depression, fear of rejection, and isolation for infected individuals during an outbreak.1 Herpes labialis is mostly caused by the herpes simplex virus-1 (HSV-1), which enters the nerve during primary infection and remains latent in the ganglionic neuron for the rest of the individual’s life. Periodically, the virus travels back down the nerve to the skin and replicates, producing a clinical episode of reactivated HSV-1 infection. Intralesional viral replication is halted by the host immune response approximately 7 days after primary infection and 3 days after recurrent infection; however, inflammation secondary to immune defense is also the cause of redness, swelling, and tenderness that is characteristic of herpes labialis lesions. As a result, although viral clearance happens rapidly following reactivation, the lesion often takes 7-10 days to heal completely.

Since the pathogenesis of herpes labialis is both viral- and immune-mediated, it is not surprising that administration of exclusively antiviral drugs has limited effects on the clinical parameters of the disease.2 Therefore, medications demonstrating dual mechanisms via inhibition of viral replication and modulation of the inflammatory response to facilitate healing, indicate a more successful therapeutic approach.3 Such an agent was introduced by Valeant Pharmaceuticals, consisting of 5% antiviral acyclovir plus 1% anti-inflammatory hydrocortisone (ACHC) in a topical cream formulation (Xerese™). Although it has been FDA-approved in the US for the treatment of recurrent herpes labialis since 2009, authorization for Xerese™ in Canada was not officially granted until October 2013. In light of this recent Canadian approval, we review the data supporting the efficacy of this topical combination therapy and discuss the details regarding its clinical use, specifically incorporating our experience in prescribing ACHC for the past half-decade.

Drug Information
ACHC is intended for the early treatment of recurrent herpes labialis (HSL) in adults and adolescents (12 years of age and older). It is designed for cutaneous use only and is applied to the lips and skin around the mouth. Usage should be avoided on the eyes, inside the mouth or nose, and on the genitals. The patient should be instructed to apply a thin layer across the affected area, including the outer margins of the cold sore. Treatment should be initiated at the first sign or symptom (prodromal stage), applying 5 times per day for a period of 5 consecutive days. If there is no noticeable improvement and/or the cold sore fails to heal within 2 weeks, patients are encouraged to seek further medical attention. At present, the efficacy of ACHC has not been established in the immunocompromised population.3

From Bench to Bedside: Duration and Efficacy
In order to obtain maximum clinical benefit from a topical antiviral medication, therapy should be initiated within 72 hours of onset of symptoms.4 Patients with recurrent herpes labialis experience a rapid onset of disease and a short viral shedding period, both of which make it difficult to measure responses to therapy.
In an early basic science study conducted in 2003, researchers used mice that had undergone adaptive transfer of immunity and infected the skin on the mice's ear pinna with HSV-1. After the mice developed a zosteriform infection, treatment groups received topical ACHC, 5% acyclovir (Zovirax®), 1% hydrocortisone, or no treatment at all. Medication was applied 3 times daily for 4 days. The treatment groups were analyzed based on ear thickness increase and zoster score. The zoster scores were adapted from a scale previously described in another study, and the scores used were: 0 for unchanged ear, 1 for isolated zosteriform lesions, and 2-4 for describing the ulceration of confluent zosteriform lesions from mild to severe. ACHC outperformed both 5% acyclovir and 1% hydrocortisone creams, with an average increase in ear thickness of 0.15 ± 0.03 mm compared to 0.48 ± 0.08 mm and 0.23 ± 0.03 mm, respectively. The average increase in ear thickness for ACHC was only 34% of that experienced by the mice in the control group, compared to 110% observed with acyclovir and 52% with hydrocortisone. The average zoster score for the ACHC group at day 9 was also the lowest of the four groups at 2.0 ± 0.2 (58% of control), compared to 2.4 ± 0.3 (70% of control) for acyclovir and 2.8 ± 0.2 (80% of control) for hydrocortisone.

In a 2012 Phase 3 study, Strand et al instructed their human subjects to apply ACHC 5 times daily for 5 days at the onset of prodromal symptoms, preferably before the appearance of actual papules or vesicles. Of the 131 test subjects, 78 (59.5%) had non-ulcerative recurrences, and 53 (40.5%) had ulcerative recurrences. At the follow-up visit, all 131 of the test subjects had returned to the stage of normal skin, 3 weeks after the last dose, with no signs or symptoms of herpes labialis recurrence. In the 40% of subjects who experienced ulcerative herpes lesions despite applying the ACHC cream, the mean maximum lesion area was 39 mm², which was a 48% decrease from the mean lesion area size of 75 mm² typically reported in immunocompetent adults.

A similar study published in 2011, also using a dosing regimen of applying cream 5 times daily for 5 days, studied a much larger patient population in a randomized, double-blind, placebo-controlled trial. The 2,437 volunteers were randomized to receive either ACHC, acyclovir in the ACHC vehicle, or placebo in the form of the ACHC vehicle. Of the 1,443 subjects who experienced a recurrence of herpes labialis during the trial and initiated treatment, 42% used ACHC, 42% acyclovir, and 16% placebo. The authors reported that 58% of the patients on ACHC developed an ulcerative lesion, vs. 65% in the acyclovir group and 74% in the placebo group. In patients who experienced an ulcerative lesion, the healing times were reduced in those who received ACHC or acyclovir, compared with placebo. The patients using ACHC also had a smaller cumulative lesion area (~50% less) than the placebo group (Tables 1 and 2).

Finally, in a simulated 2002 trial, researchers tested the efficacy of ACHC in patients whose latent HSV-1 infection was intentionally reactivated using ultraviolet (UV) light. Of the 380 subjects, 120 patients developed classical cold sores 2 days after UV light exposure, which was followed by initiation of treatment with either ACHC or placebo. Treatment with ACHC reduced lesion size, healing time, and lesion tenderness when compared with placebo. Healing time (defined as the time to restoration of normal skin) was reduced from 10.1 days in the placebo group to 9.0 days in the ACHC group (Table 2).

**Adverse Effects**

The combination cream of 5% acyclovir and 1% hydrocortisone has been shown to induce only minimal side effects when used to treat herpes labialis infections. In Strand et al's 2012 Phase 3, open-label, multicenter study, 131 of 134 subjects were categorized with recurrence at the post-treatment visit. Of these 131 subjects, only 5 reported any adverse events. The events were classified as mild to moderate in intensity and consisted of secondary herpes labialis recurrences (n=2), infectious rhinitis (n=1), application site inflammation (n=1), and bronchial asthma (n=1). Additional studies have corroborated the safety of ACHC, observing only minor side effects. The most common adverse reactions reported in clinical trials were drying or flaking of the skin, burning or tingling at the application site, erythema, and pigmentation changes; these infrequent adverse effects occurred in less than 1% of patients studied.

**Other Therapies for Herpes Labialis**

Prior to the authorization of Xerese™ by Health Canada, the mainstays of treatment for recurrent HSL included over-the-counter docosanol cream, and prescription-only members of the acyclovir family (oral and topical). If ACHC is contraindicated for use in a particular patient due to adverse effects, docosanol or acyclovir may provide therapeutic benefit.

Docosanol 10% cream (Abreva®) is an approved treatment for recurrent herpes labialis, with efficacy demonstrated in two identical double-blind, placebo-controlled studies conducted at 21 sites. Therapy was initiated at the onset of prodromal symptoms or the erythema stage in subjects who were otherwise healthy adults with documented histories of herpes labialis. Treatment was administered 5 times daily until healing occurred, with twice-daily visits to the investigative clinic for the first 7 days. For the 370 patients who were treated with docosanol, the median time to heal was 4.1 days, which was 18 hours shorter than the healing time for the 367 patients treated with placebo (Table 2). The patients treated with docosanol also reported earlier cessation of pain and exhibited complete healing, as well as experienced reduced lesion progression to the ulcer or soft crust stage.

A well-established mainstay in the treatment of recurrent herpes labialis is valacyclovir. This prodrug of acyclovir has proven to be a safe and effective therapy for long-term HSV suppression. It has been studied in children, pregnancy, and immunocompromised patients. The most common adverse events associated with oral valacyclovir are headache, rhinitis, infection, nausea, and pharyngitis, with all of these occurring infrequently. Despite many years of use by clinicians, HSV resistance remains low at approximately 0.1%-0.4% in the UK and the US.

A new form of acyclovir was recently approved by the US FDA in April 2013. This medication consists of acyclovir in the form of a mucoadhesive buccal tablet (ABT) (Sitavig®), which is applied to the upper gum region within the first hour of prodromal symptoms. A Phase 3 double-blind trial found that acyclovir, utilizing the proprietary Lauriad® technology, decreased the median duration time and development of primary vesicular lesions when compared to placebo (Tables 1 and 2).
Lastly, a non-pharmacologic treatment for recurrent HSL involves low-level light therapy. A paper published in 2013 demonstrated that 1072 nm light-emitting diode therapy applied 3 times a day for 2 days was able to shorten healing time in patients with HSL to a median of 129 hours vs. 177 hours for the control group (Table 2).16

### Clinical Observations
When taken daily (along with topical sunscreens), oral acyclovir, famciclovir, or valacyclovir are better at preventing herpes labialis than topical therapies are at treating outbreaks; however, it is the authors’ experience over the past 5 years that when used appropriately, ACHC is the superior topical therapy. Because

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**Table 1:** Comparing efficacies of therapy by percent of lesions that ulcerate

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<td></td>
<td>Placebo</td>
<td>225</td>
<td>6.5</td>
<td></td>
</tr>
<tr>
<td>Downing 2014</td>
<td>Acyclovir Lauriad®</td>
<td>376</td>
<td>5.57</td>
<td>0.003</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>395</td>
<td>6.38</td>
<td></td>
</tr>
</tbody>
</table>

**Table 2:** Comparing efficacies of therapy by median time to heal
the signs and symptoms of herpes labialis are attributable to both viral and inflammatory mechanisms, prescription topicals exerting only antiviral or anti-inflammatory activities have limited efficacy. Most over-the-counter therapies fail to target underlying pathogenic mechanisms (i.e., viral and inflammatory) and, thus, have little to no efficacy. While the optimal strategy is to prevent herpes labialis outbreaks via reduction of sun exposure, as well as through the use of sunscreen and oral anti-viral agents (especially in individuals experiencing frequent outbreaks), we recommend to our patients that they fill their prescriptions for AHC as soon as possible and keep the cream at home, at work, and/or carry it with them while on vacation. At the onset of prodromal symptoms, therapy should be initiated immediately and no later than the appearance of the first sign of a recurrence.

**Conclusion**

Herpes labialis still lacks a cure, but several options are now available to limit inflammation and decrease healing time. The introduction of 5% acyclovir/1% hydrocortisone topical cream represents a forward step in understanding disease pathogenesis and targeting both the viral and immunogenic components of recurrent HSL.

**References**

Skin Therapy Letter

Available for iPad, iPhone and iPod touch
Provides instant access to all articles published to date.
Powerful search functionality and intuitive navigation tools allow the user to find relevant information quickly.
The application is updated automatically to include the most recently published articles.

Content & instructions can be found at:
http://www.skintherapyletter.com/ipad/about.html
http://www.skintherapyletter.com/ipad/support.html

To get more information, medical professionals and consumers can access all of our sites from
www.SkinInformation.com or go directly to:

Patient sites:
- AcneGuide.ca
- CosmeticProcedureGuide.ca
- GenitalWarts.ca
- MildCleanser.ca
- RosaceaGuide.ca
- UnwantedFacialHair.ca
- ActinicKeratosis.ca
- DermatologyCare.ca
- HandEczema.ca
- MohsSurgery.ca
- SkinCancerGuide.ca
- BotoxFacts.ca
- EczemaGuide.ca
- HerpesGuide.ca
- PsoriasisGuide.ca
- SkinCoverup.com
- ColdSores.ca
- FungalGuide.ca
- Lice.ca
- PsoriaticArthritisGuide.ca
- Sweating.ca

Medical professional sites:
- Dermatologists.ca
- PASItraining.com
- SkinCareGuide.ca
- SkinTherapyLetter.ca
- SkinPharmacies.ca
- SkinTherapyLetter.com
- SkinInformation.com
<table>
<thead>
<tr>
<th>Name/Company</th>
<th>Approval Dates/Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brimonidine tartrate 0.33% topical gel</td>
<td>Health Canada approved brimonidine tartrate 0.33% gel in February 2014 for the topical treatment of the facial erythema (redness) of rosacea in adults. It is not indicated for the treatment of inflammatory lesions (papules and pustules). Brimonidine is thought to work by constricting dilated facial blood vessels to reduce the redness of rosacea. Also in February 2014, the European Commission granted Marketing Authorization in Europe for brimonidine 3 mg/g gel (Mirvaso®). Brimonidine tartrate 0.33% gel (Mirvaso®) was US FDA approved in August 2013.</td>
</tr>
<tr>
<td>Brimonidine 3 mg/g topical gel</td>
<td>Mirvaso® Galderma International</td>
</tr>
<tr>
<td>Apremilast tablets</td>
<td>In March 2014 the FDA approved the first oral therapy for the treatment of adults with active psoriatic arthritis (PsA). Apremilast is an oral small molecule inhibitor of phosphodiesterase 4 (PDE4) specific for cyclic adenosine monophosphate (cAMP). PDE4 inhibition results in increased intracellular cAMP levels, thereby suppressing immune responses. Safety and efficacy were evaluated in three clinical trials involving 1,493 patients with active PsA. Patients treated with apremilast showed improvement in signs and symptoms of PsA.</td>
</tr>
<tr>
<td>Omalizumab for SC injection</td>
<td>The FDA approved omalizumab (a recombinant humanized monoclonal antibody that blocks the high-affinity Fc receptor of immunoglobulin E) in March 2014 for the treatment of chronic idiopathic urticaria (CIU). The new use (already approved for asthma) is for patients ≥12 years of age who remain symptomatic despite H1-antihistamine therapy. Treatment is not indicated for other forms of urticaria (hives). It is the first biologic medicine and first medicine approved by the FDA for CIU since non-sedating H1-antihistamines.</td>
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<tr>
<td>Propranolol hydrochloride oral solution</td>
<td>The FDA approved the first and only beta-blocker formulation in March 2014 for the treatment of proliferating infantile hemangioma requiring systemic therapy. HemangeoTM, specifically developed for use in pediatric patients, was studied in infants aged 5 weeks to 5 months (at therapy initiation) in a randomized, double-blind placebo-controlled, multi-dose and multicenter adaptive Phase 2/3 trial, which compared four propranolol treatment protocols (1 mg or 3 mg/kg/day for 3 or 6 months) vs. placebo. The treatment protocol of 3 mg/kg/day for 6 months demonstrated a 60.4% success rate vs. 3.6% in the placebo group, achieving the primary endpoint of complete or nearly-complete resolution.</td>
</tr>
<tr>
<td>Microbicidal-coated condom</td>
<td>The Japanese Ministry of Health, Labour and Welfare granted marketing approval to Vivagel®-coated condom in March 2014. The product of nanotechnology, Vivagel® (active ingredient SPL7013) is a gel-based formulation of a proprietary dendrimer with both antibacterial and antiviral properties. In laboratory studies Vivagel® killed 99.9% of HIV, HPV, and HSV-2 (genital herpes virus).</td>
</tr>
</tbody>
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