

## Rosacea and Its Topical Management

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### ABSTRACT

Many options exist for the treatment of rosacea, including topical and systemic therapies, laser and light-based therapies, and surgical procedures. A classification system for rosacea identifies 4 subtypes (i.e., erythematotelangiectatic, papulopustular, phymatous, and ocular), which may help guide therapeutic decision-making. The goals of therapy include reduction of papules, pustules, erythema, physical discomfort, and an improvement in quality of life. Standard topical treatment agents include metronidazole, azelaic acid, and sodium sulfacetamide-sulfur. Second line therapies include benzoyl peroxide, clindamycin, calcineurin inhibitors, and permethrin.

**Keywords:** rosacea; topical therapy; systemic therapy; laser

Rosacea is a chronic relapsing skin disorder characterized by facial flushing, persistent erythema, telangiectasia, and inflammatory papules and pustules affecting the central face. The National Rosacea Society has described a classification system based on 4 main subtypes: erythematotelangiectatic, papulopustular, phymatous, ocular, and one variant, i.e., granulomatous.<sup>1</sup> Rosacea can contribute to lower self-esteem and have significant psychosocial implications, e.g., stress at work and social isolation.<sup>2</sup> This can have a significant impact on quality of life and should be taken into consideration when treating these patients.

Treatment starts with making a proper diagnosis, including identification of subtype. Following this, conservative measures, such as trigger avoidance, proper skin care, camouflaging cosmetics, and photoprotection should be discussed in detail. Topical pharmacotherapeutic options include: azelaic acid (Finacea<sup>®</sup> Gel, Intendis/Bayer), clindamycin, clindamycin 1%-benzoyl peroxide 5% gel (BenzaClin<sup>®</sup>, sanofi-aventis; Duac<sup>®</sup>, Stiefel), erythromycin, metronidazole (MetroCream<sup>®</sup>, MetroLotion<sup>®</sup>, MetroGel<sup>®</sup>, Rozex<sup>®</sup> Gel, Galderma; Noritate<sup>®</sup>, Dermik), or sodium sulfacetamide 10% + sulfur 5% (Plexion<sup>®</sup>, Medicis; Rosac<sup>®</sup> Cream, Stiefel; Rosula<sup>®</sup> Lotion, Doak Dermatologics; Sulfacet-R<sup>®</sup>, Novacet<sup>®</sup> Lotion, Perrigo). For patients with moderate-to-severe papulopustular rosacea or those with ocular involvement, systemic therapy is often prescribed and options include doxycycline, erythromycin, metronidazole, minocycline, tetracycline, or in severe cases, low dose isotretinoin. The telangiectatic component does not respond to either oral or topical therapy, and is best treated with laser and light-based therapies. Surgical intervention may be required for the phymatous subtype. Therapeutic choices will depend on patient expectations, tolerance, previous

therapies used, rosacea subtype, and severity. This article will focus on topical therapies for rosacea.

### *Azelaic Acid (AZA)*

AZA is a newer therapeutic option for the treatment of rosacea. It was approved by the US FDA in 2002, the European Union in 2003, and in Canada in 2004, although it has only recently become commercially available in Canada. AZA is a naturally occurring dicarboxylic acid that can be found in dietary sources, such as whole grains.<sup>3</sup> It lacks toxicity, is nonteratogenic and nonmutagenic.<sup>4</sup> It has multiple biologic effects including anti-inflammatory, antikeratinizing and antibacterial activities. The likely mechanism of action is via inhibition of reactive oxygen species produced by neutrophils.<sup>4</sup>

A novel 15% gel formulation (Finacea<sup>®</sup>, Intendis/Bayer) is available for the treatment of rosacea, in addition to a 20% cream formulation approved for use in acne vulgaris. The 15% gel, although formulated to a lower concentration than the cream, is significantly more bioavailable than the cream because of an optimized aqueous gel vehicle. Multiple reviews have been published examining the use of AZA in rosacea.<sup>3,5,6</sup> Two pivotal phase III trials have shown that AZA 15% gel, applied twice daily for 12 weeks, was superior when compared with the vehicle for patients with papulopustular rosacea.<sup>7</sup> A mean reduction in inflammatory lesion counts ranged from 51%–58% in the AZA group, compared with 39%–40% in the vehicle group. Improvement in erythema scores ranged from 44%–46% in patients treated with AZA, compared with 28%–29% in the vehicle group.<sup>7</sup> In a 15-week study, AZA 15% gel applied twice daily also showed significant benefit over metronidazole 0.75% gel.<sup>8</sup> In these studies, the use of AZA 15% gel led to a mean

reduction in inflammatory lesion counts ranging from 51%–73% and a reduction of erythema severity ranging from 44%–56%. The number of patients achieving success, as defined by the investigator global assessment, ranged from 61%–69%.<sup>7-9</sup>

A split-face study by Maddin<sup>10</sup> comparing AZA 20% cream with metronidazole 0.75% cream, showed a reduction in inflammatory lesions of 78.5% and 69.4%, respectively. There was also a reduction in erythema of 25.5% and 18.7% for AZA and metronidazole, respectively. Both treatments led to a significant reduction in inflammatory lesions over 15 weeks, but the difference between treatments was not significant.<sup>10</sup> Of note, the physician rating of global improvement was significantly higher on the side treated with AZA at both weeks 9 and 15.<sup>10</sup> In the comparative studies, AZA had a greater potential to cause irritation than the metronidazole, which included facial skin signs and symptoms. However, these events were reported as mild to moderate and transient in nature.<sup>8</sup> There was no improvement reported in telangiectasia severity in any study of AZA for rosacea.

The dosing recommendation for AZA 15% gel is a twice daily application. However, Thiboutot et al. found once daily dosing to be as effective as twice daily.<sup>11</sup> Research has shown that AZA when used as a treatment for papulopustular rosacea is a safe and effective and exhibits a favorable tolerability profile.

### *Metronidazole*

Metronidazole has been the mainstay of topical rosacea treatment. It is a nitroimidazole antibiotic whose mechanism of action in rosacea is not well established, but appears to work through an anti-inflammatory mechanism.<sup>12,13</sup> It is the most widely used topical agent for rosacea and is available in a 0.75% gel, lotion, and cream format for twice daily use, and a 1% cream or gel for once daily use. Jorizzo et al.<sup>14</sup> found that once daily dosing of 1% metronidazole cream was as effective as twice daily dosing. It is generally well tolerated and has a low incidence of adverse effects.<sup>12,13</sup> A recent review by the Cochrane Collaboration<sup>15</sup> and a condensed version of this work by van Zuuren et al.<sup>5</sup>, summarizes 9 “high and intermediate quality” trials, which show clear evidence that topical metronidazole is significantly more effective than vehicle alone. Most of these studies used 0.75% metronidazole and ranged from 8-9 weeks in duration, with 1 trial lasting 6 months. A reduction in inflammatory lesions and erythema scores were noted, as was an improvement in physician’s global evaluation, and patient-assessed measures when these were available.<sup>5,15</sup> No benefits were noted for the telangiectasia in these studies, however, a study by Tan et al. showed improvement in telangiectasiae scores, as well as erythema and inflammatory lesion counts, using a 1% metronidazole cream with SPF 15.<sup>16</sup>

Although data are limited, 2 studies have shown that topical metronidazole may be as effective as oral tetracycline in reducing the inflammatory component of rosacea.<sup>17,18</sup> Efficacy of metronidazole is constant regardless of the formulation, strength, and frequency of application.<sup>12</sup> This drug also plays a role in maintenance therapy, either with or without prior concomitant systemic antibiotic therapy.<sup>12</sup> Given its high efficacy and tolerability, it will continue to play an important role in the management of rosacea.

### *Sodium Sulfacetamide 10% + Sulfur 5%*

Sodium sulfacetamide 10% + sulfur 5% is an older treatment that has gained new popularity. It is used to treat acne, rosacea, and seborrheic dermatitis,<sup>13</sup> and is available in multiple formulations as a lotion, cream, gel, or cleanser.<sup>9,13</sup> The mechanism of action is not well understood, but the sulfacetamide has antibacterial properties, and the sulfur component confers antifungal, antidemodectic, and keratolytic effects.<sup>19</sup> Two studies, one comparing the sodium sulfacetamide-sulfur combination with the vehicle and another comparing it with metronidazole 0.75% gel, showed a significant reduction in both inflammatory lesion counts and erythema scores in papulopustular rosacea.<sup>19,20</sup>

### *Other Therapies*

Many other topical treatments for rosacea have been reported. Some are effective, but are not yet approved. Further investigation is needed to determine their potential role in the topical armamentarium of rosacea therapy.

- Topical antibiotics (e.g., clindamycin lotion or cream) have shown benefit, but evidence supporting their use is lacking.
- The calcineurin inhibitors, tacrolimus (Protopic®, Astellas Pharma) and pimecrolimus (Elidel®, Novartis), have been investigated for use in papulopustular rosacea because of their anti-inflammatory effects. Early reports suggested benefit from tacrolimus in the treatment of steroid-induced rosacea.<sup>21</sup> However, while 3 studies have demonstrated a reduction in erythema associated with rosacea, neither tacrolimus nor pimecrolimus had any benefit over vehicle with respect to lesion counts.<sup>22-24</sup>
- Clindamycin 1%-benzoyl peroxide 5% gel, which is approved for use in acne vulgaris, has shown promise for rosacea therapy. A double-blind, randomized controlled trial using this once daily formulation showed a significant reduction in inflammatory lesion count, erythema severity, and overall rosacea severity. The treatment was well tolerated.<sup>25</sup>
- Permethrin 5% cream, which is proposed to work because of its anti-parasitic effects, may target *Demodex* mites, a potential cause of rosacea.<sup>13</sup> This formulation was compared in 1 study with the vehicle and with metronidazole 0.75% gel, and was found to be superior to the vehicle and equal in efficacy to metronidazole.<sup>26</sup>
- Topical retinoids have been used to treat rosacea, but the true efficacy has not been established. Their use is

limited by their irritant potential. Nally and Berson<sup>13</sup> suggested that better tolerated agents, e.g., adapalene, should be considered.

- Topical steroids are sometimes used on a short-term basis for the severe inflammatory component, but long-term side-effects and exacerbating potential limit their use in this chronic condition.<sup>13</sup>
- There is anecdotal evidence of 4 patients with erythematotelangiectatic rosacea who were treated successfully with oxymetazoline, a topically applied selective  $\alpha_1$ -adrenergic receptor agonist. The impressive results of this treatment warrant further study.<sup>27,28</sup>

### Conclusions

Because of its chronic, inflammatory nature, rosacea requires continuous management. Treatment can be tailored to the subtype and may involve a combination of therapies. Patients should first be counseled on the triggers of rosacea, proper skin care, photoprotection, and camouflaging cosmetic options. Topical therapy is usually first line, but in moderate-to-severe cases, or those with ocular involvement, systemic therapy may be required. Laser or light-based treatments and surgical procedures can offer added benefit. Many topical agents are available for the treatment of rosacea, and the erythematotelangiectatic and papulopustular variants usually respond most favorably. There is good evidence that topical AZA and metronidazole are both safe and effective treatments. Other treatment options also include sodium sulfacetamide 10%-sulfur 5%, benzoyl peroxide 5%-clindamycin 1%, or clindamycin alone.

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## Drug Treatments for Skin Disease Introduced in 2008

<i>Drug Class</i>	<b>Generic/Trade Company Names</b>	<b>Indication</b>	<b>Approving Regulatory Agency</b>
<i>Actinic Keratosis</i>	<b>Methyl Aminolevulinate HCl Cream</b> <i>Metvixia™ + Aklilite® CL128</i> Photocure ASA/ Galderma	Approved for the treatment of actinic keratosis.	US FDA
<i>Antiacne Agents</i>	<b>Adapalene 0.1%</b> <i>Differin® Gel</i> Galderma KK/ Schionogi	Approved for the treatment of acne vulgaris.	Japan's Ministry of Health, Labour & Welfare
	<b>Clindamycin Phosphate 1.2% + Benzoyl Peroxide 2.5%</b> <i>Acanya® Gel</i> Arcutis Pharmaceuticals	Approved for the once daily treatment of both non-inflammatory and inflammatory acne lesions in patients 12 years of age and older.	US FDA
<i>Antibacterial Agents</i>	<b>Ceftobiprole Medocaril IV</b> <i>ZEFTERA®</i> Basilea Pharmaceuticals	Approved for the treatment of complicated skin and soft tissue infections, including diabetic foot infections. In Switzerland, this includes non-limb-threatening diabetic food infections without concomitant osteomyelitis.	Health Canada, Swissmedic
<i>Anticancer Agents</i>	<b>Denileukin Diftitox</b> <i>Ontak®</i> Esai Corporation	Approved for the treatment of patients with persistent or recurrent cutaneous T-cell lymphoma whose malignant cells express the CD25 component of the IL-2 receptor (CD25+).	US FDA
<i>Antihistamine</i>	<b>Loratadine</b> <i>Claritin®</i> Schering-Plough	Approved labeling change to advise consumers that this OTC formulation relieves allergy symptoms caused by both perennial and seasonal allergies.	US FDA
<i>Antipruritic Agent</i>	<b>Levocetirizine Dihydrochloride 0.5mg/ml Oral Solution</b> <i>Xyzal®</i> UCB & sanofi aventis	Approved for the relief of symptoms associated with indoor and outdoor allergies, and for chronic idiopathic urticaria.	US FDA
<i>Antipsoriatic Agents</i>	<b>Adalimumab</b> <i>Humira®</i> Abbott Laboratories	Approved for the treatment of adults with moderate-to-severe chronic plaque psoriasis, who are not suitable candidates for other systemic therapies.	US FDA
	<b>Calcipotriene 0.005% + Betamethasone Dipropionate 0.064% Topical Suspension</b> <i>Taclonex Scalp® / Xamiol® Gel</i> LEO Pharma/ Warner Chilcott	Approved for the once daily treatment of moderate-to-severe psoriasis vulgaris of the scalp in adults 18 years of age or older. It is being marketed as Taclonex Scalp® (Warner Chilcott) in the US and Xamiol® (Leo Pharma) in Canada & Europe.	US FDA, EMEA, Health Canada
	<b>Calcipotriene 0.005% Topical Solution</b> Nycomed US, Inc./ Fougera	Generic formulation approved for the topical treatment of chronic, moderately severe psoriasis of the scalp.	US FDA
	<b>Etanercept</b> <i>Enbrel®</i> Wyeth	Approved in a 50mg once weekly dosage regimen as an alternative to the currently approved 25mg twice weekly regimen for the treatment of moderate-to-severe plaque psoriasis.	EMEA
	<b>Ustekinumab</b> <i>Stelara®</i> Janssen-Ortho	Approved for adults with moderate-to-severe plaque psoriasis.	Health Canada

<b>Drug Class</b>	<b>Generic/Trade Company Names</b>	<b>Indication</b>	<b>Approving Regulatory Agency</b>
<i>Crohn's Disease</i>	<b>Certolizumab Pegol</b> <i>Cimzia</i> <sup>®</sup> UCB S.A.	Approved for the treatment of adults with moderate-to-severe Crohn's Disease who are inadequate responders to conventional therapies.	US FDA
	<b>Natalizumab</b> <i>TYSABRI</i> <sup>®</sup> Elan Corp. & Biogen Idec	Approved for inducing and maintaining clinical response and remission in adult patients with moderately to severely active Crohn's Disease (CD) with evidence of inflammation. Indicated for patients who are an inadequate responders to, or are able to tolerate, conventional CD therapies and TNF-alpha inhibitors.	US FDA
<i>Dermal Filler</i>	<b>Hyaluronic Acid Gel + Lidocaine</b> <i>Prevelle Silk</i> <sup>™</sup> Mentor Corporation/Genzyme Corporation	Approved for the reduction of moderate-to-severe facial lines, folds, and wrinkles.	US FDA
<i>Hand Eczema</i>	<b>Alitretinoin</b> <i>Toctino</i> <sup>®</sup> Basilea Pharmaceuticals	This once daily, oral treatment was approved for adults with severe, chronic hand eczema that is unresponsive to potent topical corticosteroids.	Danish Medicines Agency, French Regulatory Authority
<i>HIV/AIDS</i>	<b>Atazanavir Sulfate</b> <i>REYATAZ</i> <sup>®</sup> Bristol-Myers Squibb	Approved as part of a combination therapy in treatment naïve HIV-1 infected adult patients. This 300mg once daily formulation to be boosted with ritonavir 100mg once daily.	US FDA
	<b>Etravirine</b> <i>Intelence</i> <sup>™</sup> Tibotec Therapeutics	Approved for the treatment of HIV infected adults who have failed other antiretroviral therapies. For use in combination with other antiretroviral agents.	US FDA
	<b>Maraviroc</b> <i>SELZENTRY</i> <sup>®</sup> Pfizer	Approved for use in treatment-experienced adults with CCR5-tropic HIV in combination with other antiretroviral agents.	US FDA
	<b>Tipranavir</b> <i>Aptivus</i> <sup>®</sup> Boehringer-Ingelheim	Approved with dosing information for treatment-experienced pediatric patients aged 2-18 years who are infected with HIV. The recommended dose for both the capsules and oral solution is 14mg/kg with 6mg/kg ritonavir, or 375mg/m <sup>2</sup> tipranavir coadministered with 150mg/m <sup>2</sup> ritonavir. Prescribers should calculate the appropriate dose for each child based on body weight (kg) or body surface area (m <sup>2</sup> ) and should not exceed the recommended adult dose of 500mg coadministered with 200mg ritonavir twice daily.	US FDA
<i>Hypotrichosis</i>	<b>Bimatoprost Ophthalmic Solution</b> <i>LATISSE</i> <sup>®</sup> 0.03% Allergan	Approved once daily for hypotrichosis of the upper eyelashes. To maintain the effect, once daily continued treatment is required.	US FDA
<i>Vaccines</i>	<b>Shingles Vaccine</b> <i>Zostavax</i> <sup>®</sup> Merck Frosst	Approved for the prevention of shingles in individuals aged 60 years or older.	Health Canada
	<b>HPV Vaccine</b> <i>Gardasil</i> <sup>®</sup> Merck & Co.	An additional indication was approved, including the prevention of vaginal and vulvar cancer caused by HPV types 16 and 18 in girls and women aged 9 to 26 years.	US FDA

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Name/Company	Approval Dates/Comments
<b>Alitretinoin</b> <i>Toctino</i> ® Basilea Pharmaceuticals	The French regulatory authority approved this retinoid in October 2008 for the treatment of severe chronic refractory hand eczema unresponsive to potent topical corticosteroids in adults. Also approved by the Danish Medicines Agency in Sep 2008. Marketing applications for this product are also under review in Canada and Switzerland.
<b>Denileukin Diftitox</b> <i>Ontak</i> ™ Esai Corporation	The US FDA approved this solution for intravenous injection in October 2008 for the treatment of patients with persistent or recurrent cutaneous T-cell lymphoma whose malignant cells express the CD 25 component of the IL-2 receptor (CD25+).
<b>Bimatoprost Ophthalmic 0.03% Solution</b> <i>LATISSE</i> ® Allergan	The US FDA approved this ophthalmic solution in Dec 2008 as a novel treatment for hypotrichosis of the eyelashes.
<b>Maraviroc</b> <i>SELZENTRY</i> ® Pfizer	The US FDA approved this CCR5 antagonist in November 2008 for use in treatment-experienced adults with CCR5-tropic HIV-1 in combination with other antiretroviral agents.
<b>Clindamycin Phosphate 1.2% + Benzoyl Peroxide 2.5%</b> <i>Acanya</i> ® Gel Arcutis Pharmaceuticals	The US FDA approved this fixed combination antibiotic and benzoyl peroxide formulation in November 2008 for the once daily treatment of both non-inflammatory and inflammatory acne lesions of acne in patients 12 years of age and older.
<b>Etanercept</b> <i>Enbrel</i> ® Wyeth	The European Medicines Agency (EMA) approved this product in January 2009 for the treatment of chronic severe plaque psoriasis in children aged 8 years and above.

### Drug News

EMD Serono Canada issued new safety information in December 2008 for efalizumab (Raptiva®). This product has been associated with a risk of serious infections, including progressive multifocal leukoencephalopathy, a rare and sometimes fatal brain disorder. Efalizumab suppresses the body's immune responses in order to reduce psoriatic inflammation, thus increasing the risk of infection in some patients. In October 2008 the US FDA announced that this product would require a black box warning about this risk of infection.

The US FDA issued a complete response letter in November 2008 to Johnson & Johnson Pharmaceutical Research for ceftibiprole for the treatment of complicated skin and skin structure infections including diabetic foot infections. In 2 large multinational, double-blind, randomized phase III clinical studies, this formulation showed that it was effective and met the primary endpoint using a 10% noninferiority margin. The safety profile was consistent with the cephalosporin class of antibiotics. However, the FDA indicated from their sponsor/ monitor inspection that there was a failure to ensure proper monitoring of the studies. The FDA requested information on the clinical quality assurance programs and also asked for a new audit plan that addresses deficiencies in contract research organization monitoring. The FDA further indicated that they will not review the clinical data included in the submitted complete response until issues of data integrity have been resolved. Johnson & Johnson must fully respond to this action letter within 1 year.