

Advances in Acne and Rosacea Therapy

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■ Abstract

New topical therapies have demonstrated efficacy in patients with moderate or severe acne who might otherwise have required therapy with systemic antibiotics or isotretinoin. Increasing knowledge about the pathogenesis of acne has facilitated the development of therapies with novel modes of action. New and investigational therapies also are available or in development for the treatment of both the papulopustular and erythematous manifestations of rosacea.

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■ Keywords

Acne; adapalene; azelaic acid; ivermectin; rosacea; topical minocycline; truncal acne

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Overview

Patients with moderate or severe acne that does not respond to topical therapies often receive systemic antibiotic therapy or isotretinoin. The American Academy of Dermatology (AAD) guidelines for management of acne recommend limiting the duration of systemic antibiotics and avoiding monotherapy with them to reduce the risk of antibiotic resistance (see **Revisiting Antibiotic Treatment**).¹ Topical therapy that can improve moderate to severe acne without the need for systemic antibiotics or oral isotretinoin is needed. New topical therapies have demonstrated efficacy in up to half of patients with severe acne.^{2,3} A new treatment has been studied in truncal acne as well (see **Truncal Acne**).⁴ Investigational therapies with novel mechanisms of action in acne include a topical nitric-oxide-releasing macromolecule,⁵ a melanocortin receptor-5 antagonist,⁶ and an antiandrogen cream (CB-03-01 1%).⁷

New therapies for rosacea include a 15% foam formulation of azelaic acid, an antiparasitic agent (ivermectin 1% cream), an α_1 -adrenergic receptor agonist (topical oxymetazoline hydrochloride cream 1%), and a cationic antimicrobial peptide (omiganan). Separate formulations of topical minocycline are in development for acne and rosacea.

Revisiting Antibiotic Treatment

The current AAD guidelines and a recent consensus statement from the Global Alliance to Improve Outcomes in Acne recommend limiting antibiotic use in acne therapy to reduce the risk of antibiotic resistance, as follows^{1,8}:

- Use topical and systemic antibiotics in combination with nonantibiotic therapies (eg, topical benzoyl peroxide [BPO], topical retinoids)
 - Monotherapy with antibiotics is not recommended
- Use systemic antibiotics for the shortest possible duration, with reevaluation after 3 to 4 months
 - Evaluate response time in 6 to 8 weeks⁸

Truncal Acne

Approximately half of patients with acne have disease manifestations on the back and/or chest.⁹ Because patients may incorrectly report no acne in these areas, physical examination by the clinician is mandatory.¹⁰ The difficulty of applying topical therapies to all of the affected truncal areas, and the time required to do so, can complicate use of this approach. For this reason, oral therapies are often prescribed for truncal acne in clinical practice. However, their use is limited by AAD guidelines meant to reduce the risk of antibiotic resistance (see **Revisiting Antibiotic Treatment**).¹

A recent open-label study evaluated the efficacy of azelaic acid 15% foam in moderate truncal acne. Twice-daily foam application resulted in a 1-grade reduction on the 5-grade Investigator Global Assessment (IGA) scale for 16 of 18 patients with acne. After 16 weeks of therapy, 8 of 18 patients (44%) were judged to be clear or almost clear. The medication also improved facial acne.⁴

What's New in Acne?

Approved Agents

Adapalene 0.3% /benzoyl peroxide 2.5% (ADAP 0.3%/BPO 2.5%) gel. In a randomized, double-blind study on ADAP 0.3%/BPO 2.5% applied once daily, about one-third of patients with moderate or severe inflammatory acne achieved an IGA score of clear/almost clear with at least a 2-grade improvement on the IGA scale at week 12 (**Table 1**).^{3,11-13} The mean reduction in baseline in inflammatory and noninflammatory lesion counts was significantly greater with ADAP 0.3%/BPO 2.5% than with vehicle. Skin irritation (2.8%) and a burning sensation (0.9%) were the most common treatment-related adverse events (AEs).³

Improvements also occurred among patients with severe acne at baseline. Nearly one-third of these patients demonstrated at least a 3-grade improvement to clear/almost clear on the IGA scale at 12 weeks with single-agent topical therapy (31.9% vs 11.8%; 95% confidence interval, 6.0%-34.2%; $P=0.029$).³

Clindamycin 1.2% /BPO 3.75% gel. This therapy demonstrated efficacy compared with vehicle in a randomized trial of patients with moderate or severe acne (**Table 1**).¹¹ More than half (55.1%) of patients with severe acne attained at least a 2-grade reduction in Evaluator Global Severity Score (EGSS) at week 12.² The overall rates of treatment-emergent adverse events (TEAEs) with active therapy in the main trial and both subgroups (severe acne and adolescents) were similar to that of vehicle.^{2,11,14}

Dapsone 7.5% gel. This agent, applied once daily, has demonstrated efficacy in two identically designed randomized, vehicle-controlled studies in adults and adolescents with moderate acne (**Table 1**).^{12,13} The rate of TEAEs was similar for dapsone 7.5% gel and vehicle.^{12,13}

Investigational Therapies

Sarecycline is a once-daily, oral, narrow-spectrum, tetracycline-derived antibiotic with anti-inflammatory properties. At 1.5 and 3.0 mg/kg, it significantly reduced inflammatory lesion counts from baseline compared with placebo (by 52.7%, 51.8%, and 38.3%, respectively), with no significant difference from placebo in noninflammatory lesion counts in a phase 2 trial of patients with moderate or severe acne. The rate of TEAEs was similar across treatment groups. AEs leading to discontinuation from sarecycline and considered treatment-related were hypoesthesia, increased

creatine phosphokinase, and decreased white blood cell count. The 1.5-mg/kg dose has entered phase 3 development.¹⁵

SB204. This agent contains a nitric oxide-releasing macromolecule formulated in an alcoholic gel.¹⁶ Nitric oxide has been shown to inhibit *Propionibacterium acnes* growth as well as *P acnes*-stimulated release of interleukin (IL)-1-beta and other cytokines.⁵ Once-daily therapy with SB204 4% significantly reduced the percentage of inflammatory lesions from baseline by week 4 and the absolute inflammatory and noninflammatory lesion count at week 12, compared with vehicle, in subjects with moderate or severe acne.¹⁷ A study including patients with mild disease produced similar findings.¹⁶ The rate of TEAEs was similar across treatment groups. The rate of IGA success (clear/almost clear and ≥ 2 -grade improvement vs baseline) with SB204 4% was low (2.0%) and did not differ from that of vehicle (1.9%).¹⁶

Topical olumacostat glaseretil (OG) 7.5%. Following an announcement that this agent did not meet any of its coprimary endpoints in two phase 3 trials, development of this therapy is not proceeding at the time of this writing.

Melanocortin receptor-5 antagonist (MTC896). A phase 2, dose-ranging study of MTC896 delivered in a topical gel and applied twice daily is ongoing.¹⁸

Topical minocycline. Minocycline 4% foam applied once daily demonstrated efficacy in a phase 2, 12-week-long trial ($N=139$; moderate or severe acne). More than one-third of patients (36.2%) achieved at least a 2-grade improvement on the IGA scale at week 12 with topical minocycline, compared with 15.2% for vehicle ($P=0.021$). Topical minocycline 4% foam produced a significantly greater mean percentage reduction from baseline in inflammatory and noninflammatory lesion count compared with vehicle. Tolerability did not differ significantly between treatment groups.¹⁹

In two identical phase 3 studies of this agent ($N=466$, $N=495$), the change from baseline to week 12 in absolute inflammatory lesion count for topical minocycline 4% foam was significantly greater than that observed with a foam vehicle. The other coprimary endpoint—IGA score of clear or almost clear plus at least a 2-grade improvement from baseline—was significant in only one of the two phase 3 studies.²⁰

■ **TABLE 1** New Therapies for Acne: Efficacy Data

Agent	Study Population	Results (12 weeks)
ADAP 0.3%/BPO 2.5% gel once daily vs vehicle ³	N=503; 50:50 moderate:severe acne	Clear/almost clear and ≥ 2 -grade IGA improvement: 33.7% active therapy; 11.0% vehicle ($P<0.001$)
Clindamycin 1.2%/BPO 3.75% gel once daily vs vehicle ¹¹	N=498; 82.7% with moderate acne	Change in inflammatory lesion counts: 60.6% vs 31.4% with vehicle ($P<0.001$) Noninflammatory lesion counts: 51.6% vs 27.4% with vehicle ($P<0.001$) 34.3% vs 15.6% with vehicle achieved ≥ 2 -grade reduction in EGSS ($P<0.001$)
Dapsone 7.5% gel vs vehicle ^{12,13}	N=2,238 and N=2,102 aged ≥ 12 years, moderate acne	GAAS, 0 or 1: 29.9% and 29.8%, respectively, with dapsone vs 21.2% and 20.9%, respectively, with vehicle ($P<0.001$) Total lesion count decreased by 48.7% and 48.9%, respectively, vs 42.4% and 43.2% with vehicle ($P<0.001$)

ADAP=adapalene; BPO=benzoyl peroxide; EGSS=Evaluator Global Severity Score; GAAS=Global Acne Assessment Score; IGA=Investigator Global Assessment. Sources: Stein Gold L, et al³; Pariser DM, et al¹¹; Stein Gold LF, et al¹²; Eichenfield LF, et al.¹³

A phase 3 trial is ongoing.²¹ A phase 2b, 12-week-long, dose-ranging trial of a topical minocycline gel (1% or 2% vs vehicle) in patients with moderate or severe inflammatory acne has been completed.²²

CB-03-01 1% cream. In an 8-week, phase 2 trial, this once-daily antiandrogen cream was statistically superior to placebo at 8 weeks in terms of total lesion count, inflammatory lesion count, and acne severity index (N=77 men; mild to moderate acne).⁷ It was not superior to placebo in its effect on IGA score.²³ Phase 3 studies are in progress.^{24,25}

What's New in Rosacea?

New Topical Agents

Azelaic acid (AZA) 15% foam. Significantly higher proportions of patients achieved an IGA score of clear/almost clear plus at least a 2-point improvement at week 12 with AZA foam than with vehicle (**Table 2**).²⁶⁻³⁰ Change in inflammatory lesion count also was significantly greater with AZA 15% foam (-13.2 ± 9.5 vs -10.3 ± 9.8 ; $P < 0.001$). Application-site pain, pruritus, and dryness were reported more frequently with AZA 15% foam than with vehicle.²⁶

Ivermectin 1% cream. Significantly higher proportions of those treated with ivermectin 1% cream achieved IGA scores of clear/almost clear compared with vehicle, in two 12-week studies (**Table 2**).^{27,28} Dermatologic AEs were less common with ivermectin than with vehicle.²⁷ The rate of treatment-related dermatologic AEs was numerically lower with ivermectin 1% cream in a long-term extension trial of both studies (7.8% vs 12.9%, and 9.8% vs 16.3%; ivermectin and vehicle, respectively). Statistical comparisons were not performed.²⁸

Ivermectin cream and brimonidine gel have reduced papulopustular lesions and erythema, respectively.^{27,31} More than 60% of subjects with moderate or severe rosacea randomized to concomitant therapy with both agents for 12 weeks (ivermectin 1% cream, brimonidine 0.33% gel) attained IGA scores of clear/almost clear at the end of treatment (week 12; 3 hours after brimonidine application [61.2% vs 36.8% with vehicle, respectively; $P = 0.007$]). Half of the patients who received ivermectin 1% cream for 12 weeks with vehicle gel for 4 weeks and brimonidine gel for 8 weeks attained clear/almost clear IGA scores at 12 weeks.³²

Topical oxymetazoline hydrochloride cream 1%. An α_{1A} -adrenergic receptor agonist that causes vasoconstriction of the skin microvasculature, this agent received US Food and Drug Administration approval in January 2017 for persistent facial erythema associated with rosacea in adults. Significantly larger proportions of patients achieved at least a 2-grade improvement on both the Clinician Erythema Assessment (CEA) and Subject Self-Assessment (SSA) after 29 days of treatment with oxymetazoline hydrochloride cream compared with vehicle, in two pivotal phase 3, vehicle-controlled studies in patients with moderate or severe facial erythema of rosacea (**Table 2**).^{29,30}

Investigational Therapies

Omiganan (CONTRols001). A synthetic, cationic antimicrobial peptide, omiganan is in phase 3 development for the treatment of severe papulopustular rosacea.³³⁻³⁶

Topical minocycline. Three topical minocycline products are under study for the treatment of rosacea. In a phase 2, randomized, vehicle-controlled study, topical minocycline 1.5% and 3% foam each reduced the inflammatory lesion count significantly more than vehicle after 12 weeks of therapy in a study population of 232 patients with moderate to severe facial papulopustular rosacea (21.1 and 19.1 vs 7.8, respectively; $P < 0.001$). Significantly more patients receiving active therapy achieved IGA scores of clear/almost clear and at least a 2-grade IGA improvement at week 12 (41.8%, 33.3%, and 17.9%; 1.5% and 3.0% topical minocycline foam and vehicle, respectively; $P < 0.01$). Rates of patients reporting treatment-related AEs were 2.5%, 5.3%, and 6.4%, with topical minocycline 1.5% and 3% foam, and vehicle, respectively. No serious treatment-related AEs were reported.³⁷ A phase 3 study and a long-term safety study of the 1.5% formulation are underway.^{38,39}

Two topical minocycline gels are in phase 2 or phase 1/2 studies in patients with moderate to severe papulopustular rosacea.^{39,40}

Summary

New and investigational topical therapies are expanding the options for patients with moderate or severe acne, potentially enabling a larger number of patients to avoid systemic antibiotic or isotretinoin therapy. New treatments are increasing the options for rosacea as well.

TABLE 2 New Therapies for Rosacea: Efficacy Data

Agent	Study Population	Results
Azelaic acid 15% foam twice daily vs vehicle ²⁶	N=961; moderate or severe PPR	12 weeks: Clear/almost clear and ≥ 2 -grade IGA improvement: 32.0% vs 23.5% with vehicle ($P < 0.001$)
Ivermectin 1% cream vs vehicle once daily ^{27,28}	N=683 and N=688; moderate or severe PPR; 12 weeks	12 weeks: Clear/almost clear: 38.4% and 40.1% vs 11.6% and 18.8% with vehicle ($P < 0.001$) 40 weeks (N=622, N=636) ^a : Clear/almost clear: 71.1% and 76.0%
Topical oxymetazoline hydrochloride cream 1% vs vehicle ²⁹	N=440; moderate or severe facial erythema of rosacea	CEA and SSA success ^b ; day 29, hours post dose (active therapy vs vehicle): 3 hours: 11.9% vs 5.5%; $P < 0.05$; 6 hours: 15.5% vs 8.3%; $P < 0.05$; 9 hours: 17.7% vs 6.0%; $P < 0.001$; 12 hours: 14.8% vs 6.0%; $P < 0.01$
Topical oxymetazoline hydrochloride cream 1% vs vehicle ³⁰	N=445; moderate or severe facial erythema of rosacea	CEA and SSA success ^b ; day 29, hours post dose (active therapy vs vehicle): 3 hours: 14.3% vs 7.4%; $P < 0.05$; 6 hours: 13.4% vs 4.8%; $P < 0.01$; 9 hours: 15.5% vs 8.5%; $P < 0.05$; 12 hours: 12.3% vs 6.1%; $P < 0.05$

CEA=Clinician Erythema Assessment; PPR=papulopustular rosacea; SSA=Subject Self-Assessment.

^aLong-term extension of the two 12-week studies.

^bDefined as ≥ 2 -grade decrease (composite success) from baseline on both the CEA and SSA at 3, 6, 9, and 12 hours post dose on day 29.

Sources: Draelos ZD, et al²⁶; Stein Gold L, et al²⁷; Stein Gold L, et al²⁸; Kirck LH, et al²⁹; Baumann L, et al.³⁰

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