

Cutaneous Tolerability of Metronidazole Topical Gel, 0.75% for Rosacea

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Topical metronidazole has been available for clinical use in the United States for more than 15 years. Clinical trials evaluating metronidazole topical gel, 0.75%; metronidazole topical lotion, 0.75%; metronidazole topical cream, 0.75%; and metronidazole cream, 1% formulations are inclusive of more than 550 actively treated patients. Two recent studies gauging both the conventionally used 0.75% water-based gel and a 1% gel in a novel aqueous formulation are inclusive of more than 1800 patients. Although individuals with rosacea often exhibit an increased propensity to experiencing signs and symptoms of skin irritation, such as erythema, stinging, and burning, all currently available topical metronidazole vehicle formulations have demonstrated excellent tolerability profiles. This article reviews available data relevant to the cutaneous tolerability of topical metronidazole and reports on the results from a clinical study examining the frequency and severity of application site reactions to topical metronidazole used as monotherapy or in combination with other topical agents.

Topical metronidazole has demonstrated marked superiority as compared to vehicle in multiple, controlled, randomized studies as reviewed by McClellan and Noble,¹ Del Rosso,² and Pelle.³ A total of 10 double-blind, randomized trials were reviewed, including 8 parallel group and 2 split-face studies performed over a duration range of 7 to 12 weeks. Results from these trials showed reductions in inflammatory lesions after topical metronidazole use ranging from 48% to 65%, which exceeded reductions resulting from vehicle use in individual studies by 20% to 50%. Marked reductions in

erythema and symptoms of rosacea also were observed, with improvements reported in 54% to 88% of patients treated with topical metronidazole. Clinical evidence of improvement has been reported to occur as early as 3 weeks after starting therapy, with further benefit noted with continued use.¹ A recent, multicenter, open-label trial evaluating 612 patients with mild to moderate papulopustular rosacea treated for 12 weeks with metronidazole topical gel, 0.75% provides additional community-based experience confirming efficacy, safety, and favorable tolerability (J.Q.D., unpublished data, 2005). Efficacy results indicated a 44%, 61%, and 71% decrease in inflammatory lesions by weeks 4, 8, and 12, respectively, which were statistically significant at all time points ($P < .0001$). A decrease of 45% in mean combined facial erythema score by week 12 ($P < .0001$), improvement in telangiectasia index ($P < .0001$), and significant improvement from baseline in several quality of life indices ($P < .0001$) also were observed (J.Q.D., unpublished data, 2005).

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PERCEPTIONS RELATED TO VEHICLE TYPES: A PARADIGM SHIFT

The availability of a variety of vehicle formulations of metronidazole allows for selection based on individual preferences, prescribing habits, and the perceived need to adjust for specific skin and complexion types. In the past (especially with regard to common facial dermatoses such as acne and rosacea) formulation adjustment became particularly necessary when some vehicles, such as alcohol-based solutions and alcohol- or acetone-based gels, were associated with a high incidence of marked skin irritation. For example, tretinoin, in its conventional gel vehicle formulation, has a far greater potential for causing marked skin irritation compared with newer emollient creams and microsphere gels. The older gel and solution formulations used with several medications such as tretinoin, topical antibiotics, and benzoyl peroxide generally were reserved for patients with very oily skin.

Major advances in formulation science have allowed for the development of aqueous-based gels that can be applied to essentially all skin types. These newer gel vehicles do not carry the stigma of predictable irritation, dryness, and/or peeling that characteristically has been associated with the term *gel*. Examples include metronidazole, clindamycin, and adapalene. Following are details supporting this concept in relation to the aqueous-gel vehicle used in the metronidazole topical gel, 0.75% formulation.

TOLERABILITY REVIEW OF METRONIDAZOLE TOPICAL GEL, 0.75% Clinical Trials

A review of local skin tolerability results from multiple studies evaluating metronidazole topical gel, 0.75%; metronidazole topical cream, 0.75%; and metronidazole topical lotion, 0.75% formulations indicates a low rate of reported reactions, including stinging, burning, itching, and dryness, which generally occur in 2% or less of patients.¹⁻³ Overall evaluation of available data suggests that all 3 vehicle formulations are comparably adaptable to all skin and complexion types in patients with rosacea, with all 3 formulations reported to exhibit a low risk of tolerability reactions.¹⁻³

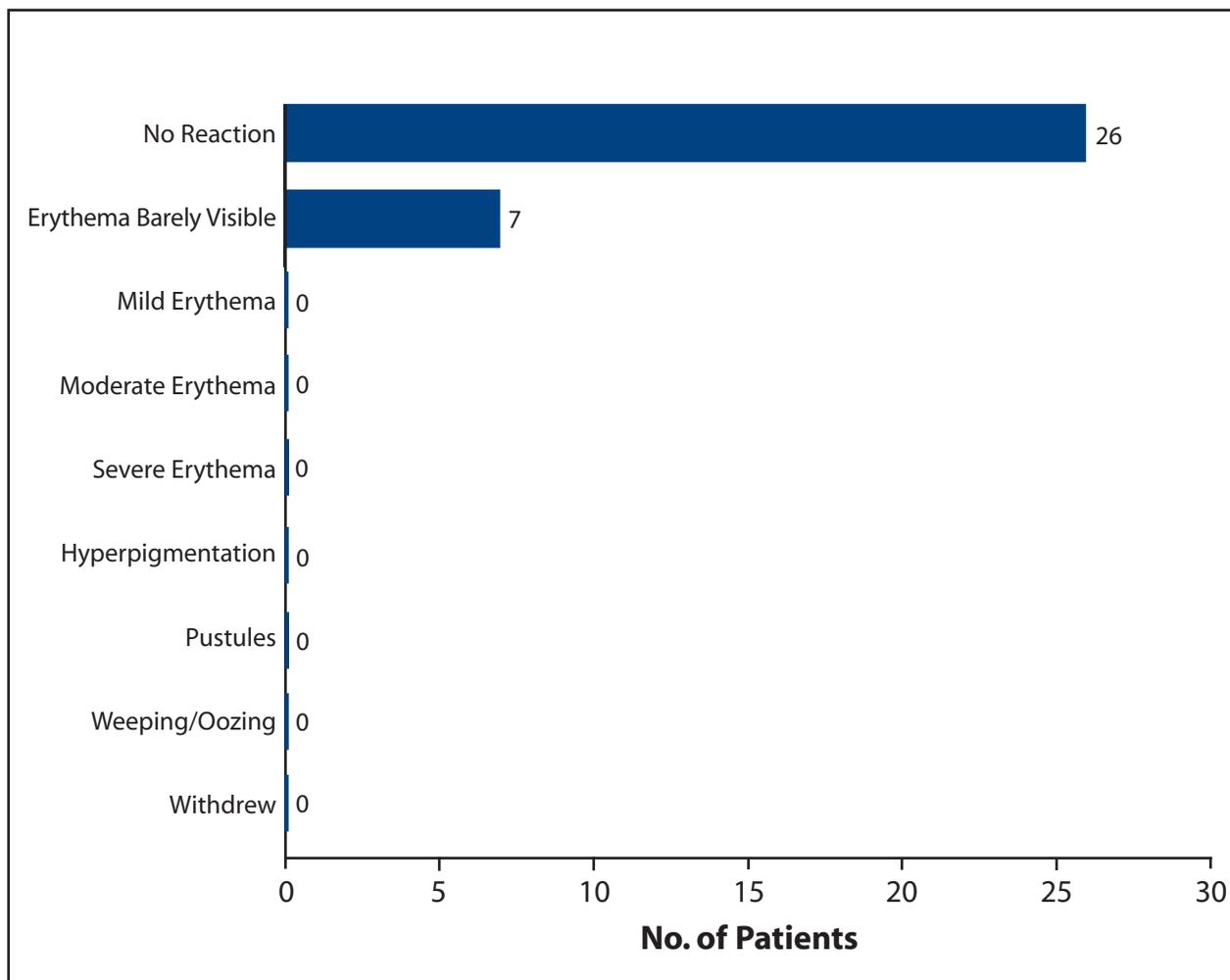
A randomized, double-blind, vehicle-controlled, 12-week, split-face study gauged the efficacy and tolerability of metronidazole topical gel, 0.75% versus vehicle applied twice daily.⁴ The study included adult men and women with moderate to severe rosacea presenting with bilateral, symmetric facial involvement with papules, pustules, and erythema (N=40). Although reduction in lesions and rosacea-associated erythema were greater on the sides treated with active drug, a decrease in rosa-

cea-associated symptoms reported at baseline, such as dryness, itching, burning, and stinging, was observed on both the sides treated with the metronidazole topical gel, 0.75% and those sides treated with the gel vehicle. Skin tolerability in both study arms was excellent; one patient reported a tearing response when the gel was applied to the periocular area.⁴

A similarly designed split-face study completed in a comparable inclusion group of adults with rosacea (N=47) indicated that stinging, burning, itching, and dryness improved over time in both the sides treated with metronidazole topical gel, 0.75% and those treated with the aqueous-gel vehicle alone. Favorable findings spotlighting reduction in disease-associated cutaneous signs and symptoms and a low incidence of local tolerability reactions were attributed to the water-based properties of the gel vehicle and the use of formulation ingredients that are not associated with marked irritation potential, including use in a "sensitive skin" population such as patients with rosacea.⁵

An open-label, multicenter, 12-week trial evaluated the efficacy and tolerability of metronidazole topical gel, 0.75% applied twice daily in men and women with rosacea presenting with no fewer than 6 facial inflammatory lesions and at least moderate facial erythema (N=92).⁶ The investigators reported that "the medication was remarkably well-tolerated." Rosacea-associated symptoms present at baseline, including itching, burning, stinging, and dryness, improved markedly over the course of the study, with skin dryness showing the greatest improvement (70%) as an individual parameter. Patient perception of dryness, itching, burning, and stinging were evaluated at baseline and at each 3-week follow-up interval through week 12. Statistically significant reduction in severity of all 4 local tolerability parameters was noted as early as week 3 ($P<.05$), with progressive improvement reported at each subsequent study visit up to study endpoint ($P<.01$).⁶

In a randomized, double-blind, 15-week trial comparing the efficacy and tolerability of azelaic acid gel, 15% versus metronidazole topical gel, 0.75%, both applied twice daily, local tolerability was rated as good to excellent in 87% of patients treated with azelaic acid and in 96% of patients treated with metronidazole (N=251).⁷ Adverse effects of facial burning, stinging, and pruritus (most rated as mild or moderate and transient) were reported in 25.8% of patients treated with azelaic acid and in 7% of patients treated with metronidazole topical gel, 0.75%. None of the patients treated with metronidazole topical gel, 0.75% discontinued therapy because of drug-related negative reactions.⁷



Results of 21-day cumulative irritation study of metronidazole topical gel, 0.75% in patients with rosacea (N=33).

Data analysis from an open-label, community-based, 12-week trial (The C.L.E.A.R. Trial) evaluating the efficacy and tolerability of metronidazole topical gel, 0.75% applied twice daily in adults with rosacea (N=612) noted local tolerability reactions in 5.3%, 2.7%, and 1.4% of patients at week 4, 8, and 12, respectively (J.Q.D., unpublished data, 2005).

Cumulative Irritation Assay

A 21-day standard cumulative irritancy assay completed in adult human subjects compared results obtained with brand formulations of metronidazole topical gel, 0.75%; metronidazole topical cream, 0.75%; metronidazole cream, 1%; and petrolatum (N=33). Under the study conditions, results indicated no statistically significant differences between the formulations, and no substantial irritation occurred following application of the

metronidazole 0.75% formulations.⁸ A recently completed 21-day cumulative irritancy assay confirmed previous findings with metronidazole topical gel 0.75%, with 26 patients demonstrating no reaction and 7 patients exhibiting barely visible erythema (Figure).⁹

Results of the 2 cumulative irritancy assays discussed correlate with clinical findings observed in multiple studies and from practice-based experience indicating that metronidazole topical gel, 0.75%: (1) is well-tolerated, (2) is not associated with a marked potential for producing skin irritation, and (3) does not exacerbate rosacea-associated symptoms or visible signs of disease (eg, scaling, erythema).^{1-4,8,9} Although the validity of cumulative irritancy assay testing has been questioned, primarily because of the application of study material to nondiseased back skin, results from such assays have correlated with clinical findings, as evidenced by results

reported with topical retinoid formulations. Results of cumulative irritancy testing also have maintained a continued position of recognition among officials involved in drug evaluation.

Combination Therapy

A review of observational experience included efficacy and safety results in adults with rosacea (N=73) who were treated with metronidazole topical gel, 0.75% twice daily with sulfacetamide 10%-sulfur 5% cleanser (n=31) or metronidazole topical gel, 0.75% once daily in the evening with either sulfacetamide 10%-sulfur 5% with sunscreens cream once daily in the morning (n=22) or sulfacetamide 10%-sulfur 5% topical suspension once daily in the morning (n=20).¹⁰ All patients were advised of proper skin care, were dispensed a designated gentle cleanser and moisturizer, and received brand formulations of both medications and skin care products. Overall, 11% of patients (8/73) experienced dryness, 5% of patients (4/73) reported mild peeling or scaling, and 8% of patients (6/73) noted transient increased erythema; in all cases, the reactions were mild, resolved within 15 minutes to 2 hours, and ultimately stopped occurring completely within 2 weeks despite continued treatment. One patient discontinued treatment because of facial redness and itching. Because both efficacy and safety findings were favorable,¹⁰ topical combination regimens warrant further evaluation.

Other trials have evaluated combination therapy with topical metronidazole. An 8-week investigator-blinded study of sulfacetamide 10%-sulfur 5% cleanser used twice daily with and without metronidazole topical gel, 0.75% reported a decrease in papule counts, erythema, and overall severity of rosacea in both study arms, with optimal response noted among patients using the combination of both active agents.² A similar efficacy trend and favorable skin tolerability were observed in a 4-week open-trial utilizing a fragrance-free sulfacetamide

10%-sulfur 5% cleanser formulation combined with topical metronidazole.¹¹

CONCLUSION

Metronidazole topical gel, 0.75% is associated with a very low incidence of local tolerability reactions and reduces rosacea-associated symptomatology (burning, itching, stinging) and visible signs of disease (erythema, dryness). The favorable tolerability profile of metronidazole topical gel, 0.75% is attributed to the aqueous-gel vehicle used in the formulation. In the treatment of rosacea, metronidazole topical gel, 0.75% is adaptable to all skin and complexion types and has a tolerability profile comparable with other metronidazole vehicle formulations, including cream and lotion.

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