A Status Report on the Medical Management of Rosacea: Focus on Topical Therapies

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Rosacea is a common inflammatory facial skin disorder estimated to affect approximately 14 million people in the United States.[1,2] About 57% of cases are diagnosed in patients younger than 50 years.[3] Although the pathophysiology of rosacea has been somewhat elusive, multiple "flare factors" are well recognized, and associated racial and genetic predilections have been identified.[1,4-7] Based on current understanding of the disease and recognized clinical presentations, a standard classification of rosacea has been suggested.[8] Therapy of rosacea has included both topical and systemic agents, with treatment regimens selected primarily based on disease severity.[2] Due to the chronic nature of the disorder, long-term maintenance therapy and avoidance of flare factors are necessary to reduce the frequency and severity of exacerbations.[9-11]

Topical metronidazole, available for clinical use since 1989, has been a "workhorse" of rosacea treatment.[2,11] Other commonly used topical therapies established through formal studies and/or accepted clinical experience include sulfacetamide 10%/sulfur 5%, clindamycin, and erythromycin.[2,12] Most recently, azelaic acid has demonstrated efficacy for treatment of rosacea.[13] Depending on the specific drug under discussion, various vehicle formulations exist. Overall, available studies demonstrate efficacy with topical therapy. Efficacy is described as a significant reduction of inflammatory lesion counts (papules, pustules) and a clinically evident decrease in erythema, with little to no effect on established telangiectasias. The following review of rosacea therapy focuses on topical metronidazole, sulfacetamide 10%/sulfur 5%, and azelaic acid.

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What is the mechanism of action of topical metronidazole?

The mechanism of action of topical metronidazole is not entirely clear.[11] In vitro studies demonstrate inhibition of inflammatory mediators generated by neutrophils.[14,15] Inhibition of neutrophil-generated reactive oxygen species and immunomodulator activity have been suggested.[14-16] A systemic mechanism is not suspected because percutaneous absorption of metronidazole is negligible.[11] The effect of metronidazole for rosacea is not believed to be associated with antibacterial or antiparasitic activity.[11,17,18]

What have efficacy studies with topical metronidazole demonstrated?

The efficacy of topical metronidazole has been established in 10 placebo-controlled studies encompassing more than 500 patients with rosacea who were actively treated with metronidazole.[11,19-28] The trials were randomized double-blinded studies in adult patients with inflammatory (stage 2) rosacea characterized by erythema, telangiectasia, papules, and pustules. Study duration ranged from 7 to 12 weeks. Split-face comparisons were used in some studies.[20,21] Topical metronidazole reduced papules and pustules by 48% to 65%, with improvements ranging from 20% to 50% greater than placebo. Reduction in erythema scores also has been demonstrated. Significant improvement for physician global assessment scores was consistently demonstrated in the topical metronidazole treatment group. Local cutaneous reactions were reported to occur in up to 2% of patients, and no significant noncutaneous reactions have been reported.[11]

How long is an adequate trial with topical metronidazole?

Although many patients note significant benefit within the first month, patients should be encouraged to complete 8 to 12 weeks of therapy before determining the extent of benefit related to topical metronidazole.[9,11]

What is the impact of drug concentration and application frequency on the efficacy and safety of topical metronidazole?

Comparable efficacy has been documented with both the 0.75% and 1% concentrations of topical metronidazole, even when used with the same frequency of application.[11,29] A comparative investigator-blinded study of metronidazole 0.75% (n=35) versus 1% (n=35) cream formulations applied once daily for 12 weeks revealed no significant difference in efficacy, with comparable reductions in lesion counts and erythema.[29] At study end point, the overall median percentage change in lesion count and overall mean percentage change in erythema was −62% and −26%, respectively, for the group treated with metronidazole 0.75%, and −60% and −30%, respectively, for the metronidazole 1% study group. Both agents were well-tolerated without significant differences identified with regard to local adverse reactions. No serious or systemic adverse reactions occurred.

Does the formulation vehicle of topical metronidazole impact on its efficacy?

The efficacy of topical metronidazole has been shown to be comparable regardless of the vehicle/formulation used.[11] Two studies in patients with moderate to severe rosacea treated twice daily for 12 weeks demonstrated comparable efficacy between metronidazole 0.75% gel and 0.75% cream and metronidazole 0.75% gel and 0.75% lotion.[30,31] No differences in efficacy were noted among any of the parameters evaluated, with reduction in inflammatory lesion counts serving as a primary evaluation parameter in both studies.

How does topical metronidazole compare with oral antibiotic therapy?

Data from 3 double-blind, double-dummy studies suggest that topical metronidazole produces efficacy comparable with low- to moderate-dose oral tetracycline therapy.[11,32-34] One 9-week study compared metronidazole 0.75% gel twice daily (n=12) with oxytetracycline 250 mg twice daily (n=15).[32] Two 8-week studies included comparisons of metronidazole 1% cream daily (n=25) versus oxytetracycline 250 mg twice daily (n=23) and metronidazole 1% cream twice daily (n=42) versus tetracycline 250 mg 3 times daily (n=50).[33,34] The benefits of oral antibiotic therapy are quicker onset of clinically evident response, shorter time to peak efficacy, and improvement of ocular rosacea. Potential disadvantages of oral antibiotic therapy are patient intolerance, potential adverse reactions, and long-term antibiotic exposure.

Do any studies support topical metronidazole as maintenance therapy?

In a 2-phase study, topical metronidazole was proven to be more effective than placebo in maintaining remission in patients with rosacea.[10] The first study phase utilized oral tetracycline 250 mg 4 times daily in combination with metronidazole 0.75% gel applied twice daily for 12 weeks (n=113). Patients exhibiting at least 70% lesion reduction after the first phase of the study were then eligible to progress to a blinded second phase of the study (maintenance therapy). The maintenance therapy phase of the study was completed during a 6-month period. Topical metronidazole 0.75% gel twice daily (n=39) was used in one patient group versus a second study arm in which patients used a topical placebo vehicle (n=43). Topical metronidazole demonstrated statistically significant superiority in maintaining remission (77% vs 58%) and reducing lesion counts compared with placebo.

What is the role of topical sulfacetamide 10%/sulfur 5%?

The anti-inflammatory benefit of sulfacetamide 10%/sulfur 5% has been reported based on clinical experience and studies.[12,35-37] Currently available preparations include "leave-on" topical suspension and lotion formulations and a skin cleanser. Although clinical efficacy and safety are established, the mechanism of action of sulfacetamide 10%/sulfur 5% in rosacea is not fully understood.

What have efficacy studies with topical sulfacetamide 10%/sulfur 5% demonstrated?

One open multicenter study was conducted to evaluate the efficacy of a twice-daily application of sulfacetamide 10%/sulfur 5% lotion over an 8-week treatment period (N=54).[35] Comparison with baseline revealed an 81% mean reduction in inflammatory lesion counts and a 43% mean reduction in erythema. This correlated with a 96% improvement in physician global evaluation and 94% improvement in patient global evaluation.

A double-blind, 8-week study (N=94) of sulfacetamide 10%/sulfur 5% lotion versus a placebo vehicle also was conducted. The active therapy group demonstrated a 65% decrease in inflammatory lesions by week 4 and a 78% reduction by week 8 versus a 44% decrease by week 4 and 36% reduction by week 8 in the placebo vehicle group. The decrease in facial erythema reported in the actively treated study arm was 66% at week 4 and 83% at week 8 compared with 33% at week 4 and 31% at week 8 in the placebo vehicle-treated group.[12]

An 8-week, investigator-blinded study compared sulfacetamide 10%/sulfur 5% lotion (n=31) with metronidazole 0.75% gel (n=32).[37] Follow-up at weeks 6 and 8 exhibited lower overall severity ratings, papule/pustules scores, and erythema ratings in patients treated with sulfacetamide 10%/sulfur 5% lotion compared with those treated with metronidazole 0.75% gel. Patient global evaluation of improvement did not differ significantly between treatment groups. Local tolerability of both agents was favorable. No significant noncutaneous adverse reactions were identified in the above studies.[12,35,37]

What is the efficacy and role of sulfacetamide 10%/sulfur 5% cleanser?

In an 8-week, investigator-blinded, controlled study, sulfacetamide 10%/sulfur 5% cleanser was used twice daily either alone (n=15) or in combination with metronidazole 0.75% gel (n=15) in patients with moderate rosacea.[38] A statistically significant reduction in papule counts and erythema was noted in both groups at all scheduled follow-up points throughout the study, and a significant reduction in the overall severity of rosacea was observed at week 8. The sulfacetamide 10%/sulfur 5% cleanser alone demonstrated efficacy as monotherapy. The combined use of the cleanser with metronidazole 0.75% gel outperformed the cleanser alone in reducing papule counts and overall rosacea severity. Treatment was well-tolerated in both study arms.

An investigator-blinded comparative tolerability study of sulfacetamide 10%/sulfur 5% cleanser (n=25) versus an established commercial, nonirritating facial cleanser (n=25) demonstrated comparable results in tested categories evaluating tolerability, irritation, and subjective assessment of product aesthetics.[39]

What is the role of topical azelaic acid?

Azelaic acid is a naturally occurring dicarboxylic acid exhibiting multiple biologic effects demonstrated in vitro and in vivo, with insignificant effects on normal cells.[40,41] Anti-inflammatory activity and effects on neutrophil activity with inhibition of reactive oxygen species may have relevance to the mechanism of action of azelaic acid therapy for rosacea.[42,43]

What have efficacy studies with topical azelaic acid demonstrated?

Two double-blind studies have established the efficacy and tolerability of azelaic acid 20% cream for treatment of rosacea.[13,43] A controlled, contralateral split-face study (N=33) of twice-daily application of azelaic acid 20% cream versus a placebo vehicle completed over 9 weeks confirmed significantly superior reduction in inflammatory lesion counts (papules, pustules), erythema index, and overall rosacea severity associated with azelaic acid use.[43] Overall, 78.2% of the face sides treated with azelaic acid exhibited complete remission or marked improvement compared with 31.2% of the sides treated with the placebo vehicle only.

A double-blind, contralateral split-face study (N=40) compared azelaic acid 20% cream with metronidazole 0.75% cream over a 15-week period in patients with symmetric papulopustular rosacea. Reduction in inflammatory lesions was comparable in both groups, with a 78.5% reduction reported on sides treated with azelaic acid and a 69.4% reduction observed on sides treated with metronidazole. Reduction in signs and symptoms of disease, including dryness and burning, also was comparable with both agents. Medication acceptability as assessed by patients was comparable in both groups. After completion of the study, 92% of patients stated they would continue therapy with azelaic acid, and 57% found azelaic acid therapy to be superior to previous medications used for treatment of rosacea.

Azelaic acid is not associated with significant noncutaneous adverse reactions.[13,43] Similar to metronidazole and sulfacetamide 10%/sulfur 5%, local cutaneous reactions, when they occur, are usually mild to moderate in intensity. Trace stinging may be seen in some patients. Stinging is characteristically transient in duration and has not been reported to result in significantly reduced compliance or discontinuation of therapy.[13,43] Published data evaluate azelaic acid 20% in a cream vehicle; however, azelaic acid 15% in an aqueous gel formulation is currently under formal evaluation to gain approval from the US Food and Drug Administration for treatment of rosacea.

Can topical agents be used in combination?

Few studies have evaluated combination therapy with topical agents for the treatment of rosacea.

The enhanced benefit of sulfacetamide 10%/sulfur 5% cleanser used in combination with metronidazole 0.75% gel was mentioned earlier.[38] Anecdotal experience suggests that combinations of topical therapy may maximize benefit in some patients, especially those demonstrating only partial response to topical monotherapy despite an adequate treatment trial.[44]

REFERENCES

1. Bamford JTM. Rosacea: current thoughts on origin. *Sem Cut Med Surg*. 2001;20:199-206.
2. Zuber TJ. Rosacea. *Prim Care*. 2000;27:309-318.
3. National Rosacea Society. Patients over 50 hardest hit with rosacea symptoms. *Rosacea Review*. Fall 2000.
4. Katz AM. Rosacea: epidemiology and pathogenesis. *J Cut Med Surg*. 1998;2:S4-S5.
5. Dahl MV. Pathogenesis of rosacea. *Adv Dermatol*. 2001;17:29-45.
6. Wilkin J. Oral thermal-induced flushing in erythematotelangiectatic rosacea. *J Invest Dermatol*. 1981;76:15-18.
7. Wilkin J. Rosacea: pathophysiology and treatment. *Arch Dermatol*. 1994;130:359-362.
8. Wilkin J, Dahl M, Detmar M, et al. Standard classification of rosacea: report of the National Rosacea Society Expert Committee on the Classification and Staging of Rosacea. *J Am Acad Dermatol*. 2002;46:584-587.
9. Wolf JE. Medication adherence: a key factor in effective management of rosacea. *Adv Ther*. 2001;18:272-281.
10. Dahl MV, Katz HI, Krueger GG, et al. Topical metronidazole maintains remission of rosacea. *Arch Dermatol*. 1998;134:679-683.
11. McClellan KJ, Noble S. Topical metronidazole: a review of its use in rosacea. *Am J Clin Dermatol*. 2000;1:191-199.
12. Sauder D, Miller R, Gratton, et al. The treatment of rosacea: the safety and efficacy of sodium sulfacetamide 10% and sulfur 5% lotion is demonstrated in a double-blind study. *J Dermatol Treat*. 1997;8:79-85.
13. Maddin S. A comparison of topical azelaic acid 20% cream and topical metronidazole 0.75% cream in the treatment of patients with papulopustular rosacea. *J Am Acad Dermatol*. 1999;40:961-965.
14. Akamatsu H, Oguchi M, Nishijima S, et al. The inhibition of free radical generation by human neutrophils through the synergistic effects of metronidazole with palmitoleic acid: a possible mechanism of action of metronidazole in rosacea and acne. *Arch Dermatol Res*. 1990;282:449-454.
15. Gnarpe H, Belsheim J, Persson S. Influence of nitroimidazole derivatives on leukocyte migration. *Scand J Infect Dis Suppl*. 1981;26:68-71.
16. Miyachi Y, Imamura S, Niwa Y. Antioxidant action of metronidazole: a possible mechanism of action in rosacea. *Br J Dermatol*. 1986;114:231-234.
17. Persi A, Rebora A. Metronidazole and *Demodex folliculorum*. *Acta Derm Venereol*. 1981;61:182-183.
18. Eriksson G, Nord CE. Impact of topical metronidazole on the skin and colon microflora in patients with rosacea. *Infection*. 1987;15:8-10.
19. Espagne E, Guillaume JC, Archimbaud A, et al. Double-blind, placebo-vehicle controlled trial of a 0.75% metronidazole gel in the treatment of rosacea. *Ann Dermatol Venereol*. 1993;120:129-133.
20. Bleicher PA, Charles JH, Sober AJ. Topical metronidazole therapy for rosacea. *Arch Dermatol*. 1987;123:609-614.
21. Aronson IK, Rumsfield JA, West DP, et al. Evaluation of topical metronidazole gel in acne rosacea. *Drug Intell Clin Pharm*. 1987;21:346-351.
22. Nielsen PG. Treatment of rosacea with 1% metronidazole cream: a double-blind study. *Br J Dermatol*. 1983;108:327-332.
23. Bjerke JR, Nyfors A, Austad J, et al. Metronidazole 1% cream v placebo cream in the treatment of rosacea. *Clin Trials J*. 1989;26:187-194.
24. Bitar A, Bourgouin J, Dore N, et al. A double-blind randomized study of metronidazole 1% cream in the treatment of acne rosacea: a placebo-controlled study. *Drug Invest*. 1990;2:242-248.
25. Breneman DL, Stewart D, Hevia O, et al. A double-blind, multicenter clinical trial comparing efficacy of once daily metronidazole 1 percent cream to vehicle in patients with rosacea. *Cutis*. 1998;61:44-47.
26. Jorizzo JL, Lebwohl M, Tobey RE. The efficacy of metronidazole 1% cream once daily compared with metronidazole 1% cream twice daily and their vehicles in rosacea: a double-blind clinical trial. *J Am Acad Dermatol*. 1998;39:502-504.
27. Drake L, Leyden J, Lucky A, et al. Evaluation of topical metronidazole cream in rosacea [abstract]. Presented at: American Academy of Dermatology 55th Annual Meeting; March 1997; San Francisco, Calif. Abstract P-65.
28. Breneman D, Bucko A, Friedman D, et al. Evaluation of topical metronidazole lotion in rosacea [abstract]. Presented at: American Academy of Dermatology 56th Annual Meeting; February 1998; Orlando, Fla. Abstract P-289.
29. Dahl MV, Jarratt M, Kaplan D, et al. Once-daily topical metronidazole cream in the treatment of the papules and pustules of rosacea. *J Am Acad Dermatol*. 2001;45:723-730.
30. Dreno B, Dubertret L, Naeyaert JM, et al. Comparison of the clinical efficacy and safety of metronidazole 0.75% cream with metronidazole 0.75% gel in the treatment of rosacea [abstract]. *J Euro Acad Dermatol Venereol*. 1998;11(suppl 2):S272-S273.
31. Guillet B, Rostain E, Powell F, et al. Metronidazole 0.75% gel and lotion are both effective in the treatment of rosacea [abstract]. *J Euro Dermatol Venereol*. 1999;2(suppl 2):S145. Abstract P-015.
32. Monk BE, Logan RA, Cook J, et al. Topical metronidazole in the treatment of rosacea. *J Dermatol Treat*. 1991;2:91-93.

33. Nielsen PG. A double-blind study of 1% metronidazole cream versus systemic oxytetracycline therapy for rosacea. *Br J Dermatol*. 1983;109:63-65.
34. Schachter D, Schachter RK, Long B, et al. Comparison of metronidazole 1% cream versus oral tetracycline in patients with rosacea. *Drug Invest*. 1991;3:220-224.
35. Davis GF, Glazer SD, Medansky RS. Successful treatment of rosacea with a novel formulation of sodium sulfacetamide 10% and sulfur 5% topical lotion. *J Geriatr Dermatol*. 1994;2:140-144.
36. Lin AN, Reimer RJ, Carter DM. Sulfur revisited. *J Am Acad Dermatol*. 1988;18:553-558.
37. Lebwohl MG, Medansky RS, Russo CL, et al. The comparative efficacy of sodium sulfacetamide 10%/sulfur 5% lotion and metronidazole 0.75% gel in the treatment of rosacea. *J Dermatol Treat*. 1995;3:183-185.
38. Swinyer L. Evaluation of a novel sodium sulfacetamide 10% and sulfur 5% prescription cleanser for the treatment of rosacea. Poster presented at: American Academy of Dermatology 59th Annual Meeting; March 2-7, 2001; Washington, DC. Poster P-147.
39. Stewart D. Assessment of tolerability of a prescription sodium sulfacetamide 10%/sulfur 5% facial cleanser in adult subjects with rosacea. Poster presented at: American Academy of Dermatology 59th Annual Meeting; March 2-7, 2001; Washington, DC. Poster P-148.
40. Nguyen QH, Bui TP. Azelaic acid: pharmacokinetic and pharmacodynamic properties and its therapeutic role in hyperpigmentary disorders and acne. *Int J Dermatol*. 1995;34:75-84.
41. Shemer A, Weiss G, Amichai B, et al. Azelaic acid (20%) cream in the treatment of acne vulgaris. *J Eur Acad Dermatol Venereol*. 2002;16:178-179.
42. Akamatsu H, Komura J, Asada Y, et al. Inhibitory effect of azelaic acid on neutrophil functions: a possible cause for its efficacy in treating pathogenetically unrelated diseases. *Arch Dermatol Res*. 1991;283:162-166.
43. Carmichael AJ, Marks R, Graupe KA, et al. Topical azelaic acid in the treatment of rosacea. *J Dermatol Treat*. 1993;4(suppl):S19-S22.
44. Del Rosso JQ. Cases about faces. *Skin Aging*. 2001;9:22-29.