

Skin Therapy Letter[©]

Volume 7 • Number 1 • January 2002

Indexed by the US National Library of Medicine and MEDLINE

EDITOR: DR. STUART MADDIN



Topical Metronidazole for Rosacea

A. K. Gupta MD^{a,b}, FRCPC, M. Chaudhry, HBS^c

^aDivision of Dermatology, Department of Medicine, Sunnybrook and

Women's College Health Sciences Center (Sunnybrook site), and the University of Toronto, Toronto, Ontario, Canada

^bMediprobe Laboratories Inc., Ontario, Canada

ABSTRACT

Rosacea is relatively common, typically occurring in individuals of Northern European and Celtic origin between 30 and 50 years of age. It is more common in women, but may be more severe in men. Currently there is no cure available for rosacea, but it can be controlled with topical and oral drug therapy. Topical metronidazole 1% cream is approved by the US FDA for the treatment of inflammatory lesions (papules and pustules) and erythema associated with rosacea. This treatment option is effective, safe and well tolerated.

Key Words: management, metronidazole, rosacea

Mechanism of Action

Metronidazole is an imidazole, and is classified as an antiprotozoal and antibacterial agent.^{1,2} Although this drug has an antimicrobial effect, it is not clear whether the beneficial effects result from direct suppression of skin bacteria.² The exact mechanism by which topical metronidazole reduces inflammatory lesions and erythema in rosacea is unknown. It is inactive *in vitro* against *Propionibacterium acnes*, staphylococci, streptococci, as well as the aerobic and anaerobic skin microflora of rosacea patients.² *In vitro* studies suggest that it is inactive against *Demodex folliculorum*.² Its anti-inflammatory effect may be due to its antioxidant action.³

Pharmacokinetics

Topical administration of metronidazole results in minimal percutaneous absorption with low systemic bioavailability.^{1,2,4} The maximum serum concentration after topical application of metronidazole 1% cream is approximately 1% of the value achieved following a single oral dose of metronidazole 250mg.¹

Clinical Trials

Metronidazole 1% Cream (Noritate[™], Dermik)

Two US multicenter, double-blind, randomized, parallel, placebo (vehicle)-controlled clinical trials established the efficacy of this cream for treating rosacea.^{5,6} Following a 10-week treatment period, patients in the metronidazole 1% treatment group had significantly fewer numbers of papules plus pustules compared to

vehicle ($P < 0.03$)⁵ (Table 1). The mean decrease in erythema severity scores from baseline was significantly greater at week 10 for the metronidazole group compared to its vehicle ($P < 0.01$). The metronidazole group showed significantly greater improvement at week 10 ($P < 0.01$) when compared to vehicle using Physician's Global Evaluation Scores. The change from baseline in the overall rosacea severity score was significantly greater ($P < 0.01$) for the metronidazole group at week 10 than the vehicle group.

In a similar study of 277 adults,⁶ 58% of those receiving Noritate[™] once-daily, showed clinical improvement of inflammatory lesions, compared to 30% for the once-daily vehicle group (Table 1). Metronidazole patients achieved a reduction in mean erythema severity scores of 41% at week 10 vs. 19% for the vehicle once-daily group.⁶ Other studies have confirmed the efficacy of metronidazole 1% cream in the treatment of rosacea.⁷

Noritate[™] is approved in the US for once daily application. The other metronidazole formulations are approved for twice-daily applications. Patient compliance may improve when fewer applications are required.⁵ Furthermore, once-daily administration may offer a lower total daily drug exposure. The moisturizing cream vehicle may also provide some relief for dry or sensitive skin.

Metronidazole 0.75% Gel (MetroGel[®], Galderma)

In a randomized split-face, double-blind, paired comparison trial, 38 patients were treated with 0.75% metronidazole gel.⁸

EDITOR-IN-CHIEF: Stuart Maddin ASSOCIATE EDITOR (International): Hugo Degreef, Catholic University, Leuven: ASSOCIATE EDITOR (Canada): Jason Rivers
INTERNET EDITOR: Harvey Lui PUBLICATIONS EDITOR: Penelope Gray-Allan EDITORIAL ADVISORY BOARD: Kenneth A. Arndt, Beth Israel Hospital & Harvard Medical School, Boston;
Wilma Fowler Bergfeld, Cleveland Clinic, Cleveland; Jan D. Bos, University of Amsterdam, Amsterdam; Enno Christophers, Universitäts-Hautklinik, Kiel; Richard L. Dobson, Medical University
of South Carolina, Charleston; Jeffrey S. Dover, Harvard Medical School, Boston; Boni E. Elewski, University of Alabama, Birmingham; Barbara A. Gilchrist, Boston University School of
Medicine, Boston; W. Andrew D. Griffiths, St. Johns Institute of Dermatology, London; Aditya K. Gupta, University of Toronto, Toronto; Vincent C.Y. Ho, University of British Columbia, Vancouver;
Mark Lebwohl, Mount Sinai Medical Center, New York; James J. Leyden, University of Pennsylvania, Philadelphia; Howard I. Maibach, University of California Hospital, San Francisco;
Larry E. Millikan, Tulane University Medical Center, New Orleans; Takeji Nishikawa, Keio University School of Medicine, Tokyo; Constantin E. Orfanos, Freie Universitäts Berlin,
Universitätsklinikum Benjamin Franklin, Berlin; Stephen L. Sacks, Viridae Clinic Sciences, Vancouver; Alan R. Shalita, SUNY Health Sciences Center, Brooklyn; Richard Thomas, Vancouver
General Hospital, Vancouver; Stephen K. Tyring, University of Texas Medical Branch, Galveston; John Voorhees, University of Michigan, Ann Arbor; Klaus Wolff, University of Vienna, Vienna

Following nine weeks of twice daily application of metronidazole gel to one side of the face and vehicle to the other, there was a mean reduction of 65.1% and 14.9%, respectively, from baseline in total papules and pustules.⁸ The reduction in erythema scores at week 9 on the metronidazole side was significantly different from scores on the placebo side ($P=0.0006$).⁸

Another clinical trial studied 19 patients with severe or recalcitrant rosacea.⁹ Patients were treated twice daily with MetroGel[®], and efficacy was determined based upon the following criteria: inflammatory lesion (papules and pustules) counts, clinical assessment of erythema and edema, and Investigator Global Assessment. The number of inflammatory lesions decreased from a mean of 20 at baseline to 7 at week 8 ($P<0.01$). Baseline erythema scores were significantly ($P<0.0001$) lower at week 8. There was also significant ($P<0.0001$) improvement in the Investigator Global Assessment scores at week 8 compared to baseline.

The efficacy of MetroGel[®] has been compared to sodium sulfacetamide 10%/sulfur 5% lotion in the treatment of rosacea.¹⁰ Fifty-five patients, applying either treatment twice daily, completed the 8-week, investigator-blinded, randomized study. The sodium sulfacetamide/sulfur treatment group experienced a significantly greater improvement than did the metronidazole group at week 8 in overall severity ($P<0.01$), reduction in papulopustule score ($P<0.01$), and reductions in mean erythema score ($P<0.05$).¹⁰

Metronidazole 0.75% Lotion (MetroLotion[®])

A 12-week clinical study was conducted in 125 patients with moderate-to-severe rosacea comparing metronidazole 0.75% lotion to its vehicle.¹¹ Applications were made twice daily to affected areas. At week 12, MetroLotion[®] was significantly more effective than vehicle in the mean percent reduction of inflammatory lesions and in the Investigators' Global Assessment of Improvement. The mean reduction of inflammatory lesion counts from baseline was 55% for MetroLotion[®] vs. 20% for the vehicle. Definite or marked improvement in the Investigators' Global Assessment of Improvement occurred in 64% of the patients in the MetroLotion[®] group compared to 35% in the vehicle group.

Metronidazole 0.75% Cream (MetroCream[®])

In a single-center, double-blind, randomized, contralateral, split-face comparison study, the efficacy and safety of topical azelaic acid 20% cream and topical metronidazole 0.75% cream was compared in 37 patients with papulopustular rosacea.¹² After 15 weeks of treatment, a significantly higher physician rating of global improvement was achieved with azelaic acid ($P=0.05$).

Metronidazole 1% Cream with Sunscreens, SPF 15 (Rosasol[®])

In a multi-center, randomized, double-blind study, twice daily application of 1% metronidazole cream with sunscreen formulation was compared to sunscreen vehicle in 120 patients with moderate-to-severe rosacea.¹³ After 12 weeks, lesion counts for the Rosasol[®] group were reduced 70% compared to 23% in the placebo group ($P=0.005$).¹³ In addition, 41% of the Rosasol[®] patients demonstrated improved facial erythema, compared to only 27% with placebo ($P=0.02$). Facial telangiectasia improved by 17% in the Rosasol[®] group vs. 4% for the vehicle group ($P=0.04$).¹³

Topical Metronidazole Versus Oral Antibiotics

In a randomized, double-blind study, 48 rosacea patients were treated for 2 months with either 1% metronidazole cream applied once daily and placebo tablets, or with 250mg oxytetracycline tablets taken twice daily and placebo (the cream base).¹⁴ After 2 months, 1% metronidazole cream was as effective as oral oxytetracycline in reducing erythema and the number of papules and pustules. Improvement occurred in 90% of patients, and there was no significant difference between the two treatments.

In a similar study with 75 patients, metronidazole 1% cream was compared with 250mg oral tetracycline taken twice daily.¹⁵ No statistically significant difference was found between the two groups after 8 weeks of treatment. However, tetracycline demonstrated a more rapid onset of effect on papules and pustules compared to the cream, and more patients treated with tetracycline obtained 100% reduction of papules and pustules.¹⁵

In a two-month, randomized, double-blind study, 101 patients were treated with either metronidazole 1% cream twice daily and placebo capsules, or placebo cream and oral tetracycline (250mg) three times daily.¹⁶ Both metronidazole 1% cream and oral tetracycline significantly reduced ($P<0.05$) the mean numbers of papules and pustules by >50% after 1 month of treatment.¹⁶

In a double-blind, randomized study, 27 rosacea patients were treated with 0.75% metronidazole gel applied twice daily and placebo capsules, or placebo (gel base) and oxytetracycline capsules (250mg) taken twice daily.¹⁷ Following 9 weeks of treatment, both treatment groups showed a reduction of >50% in papule/pustule count in all patients, with 100% clearing in 75% of the topical metronidazole group and 66% of the oxytetracycline group.¹⁷ There was no significant difference between the two treatment groups.

Topical Metronidazole and Relapse Rates

Metronidazole 1% cream was applied either once daily or once every second day for 4 months and resulted in significantly fewer relapses than 250mg oxytetracycline taken orally twice daily for two months.¹⁸ After 2 months, there was no significant difference between 1% metronidazole cream once daily and oxytetracycline therapy.

A separate study explored whether metronidazole 0.75% gel could prevent relapse of moderate-to-severe rosacea.¹⁹ Eighty-eight subjects who responded to either systemic tetracycline and topical metronidazole gel were randomized to receive metronidazole 0.75% gel or placebo. Subjects were evaluated monthly for up to 6 months and relapse was determined by the appearance of a clinically significant increase in the number of papules and pustules. In the vehicle group, 18 of 43 (42%) subjects experienced relapse, compared to only 9 of 39 (23%) subjects applying the metronidazole gel ($P<0.05$).

Adverse Effects

Adverse effects associated with topical metronidazole therapy are infrequent, but may include transient redness and mild dryness, pruritus, aggravation of rosacea or acne, burning, irritation, and stinging.² Dermatotoxicity tests have shown no evidence of contact sensitivity, phototoxicity, or photocontact allergenicity reactions.¹

Product/ Investigator	Study	n	App.	Results
Metronidazole 1% Cream: Noritate® (Dermik) • Breneman, et al ⁵	Multicenter, double-blind, randomized, parallel, 1% cream vs. placebo	139	qd for 10 wks	Overall rosacea severity score significantly greater for 1% metronidazole cream group.
• Jorizzo, et al ⁶	Multicenter, double-blind, randomized, parallel, 1% cream once daily vs. 1% cream twice daily vs. placebo	277	qd or bid for 10 wks	Using Physician's Global Assessment Scores the metronidazole qd group rated fair/better improvement (79%) vs. baseline (p<0.01).
• Bjerke, et al ⁷	Multicenter, double-blind, randomized, 1% cream vs. placebo	97	bid for 8 wks	Statistically significant difference between regimens for reducing papules plus pustules, erythema, overall assessment.
MetroGel® (Galderma): • Bleicher, et al ⁸	Double-blind, randomized, split-face, paired comparison trial, 0.75% gel vs. vehicle	38	bid for 9 wks	Erythema significantly lower than at baseline and significantly different from placebo group (P=0.006).
• Lebwohl, et al ¹⁰	Controlled, randomized, investigator-blinded, 0.75% gel vs. sodium sulfacetamide 10%/ sulfur 5% lotion	55	bid for 8 wks	Physician's Global Assessment Scores indicated consistently greater improvement in the sodium sulfacetamide/sulfur treatment group.
Rosasol® (Stiefel) • Tan ¹³	Multi-center, randomized, double-blind, 1% metronidazole + sunscreen vs. sunscreen vehicle	120	bid for 12 wks	Lesion counts showed decrease of 70% (Rosasol) vs. 23% (placebo) (P=0.005). Facial erythema showed 41% (Rosasol) vs. 27% (placebo) group (P=0.02).
Metronidazole vs Oral antibiotics: • Nielsen ¹⁴	Randomized, double-blind, 1% cream vs. 250mg oral oxytetracycline	48	1% cream: qd Antibiotic: bid for 2 mos	90% of patients showed improvement. No significant difference between 1% cream and oral antibiotics.
• Veien, et al ¹⁵	Randomized, double-blind, 1% cream vs. 250mg oral tetracycline	75	bid for 8 wks	No statistically significant differences found between the two groups.
• Schachter, et al ¹⁶	Multicenter, randomized, double-blind, 1% cream vs. 250mg oral tetracycline vs. vehicle	101	1% cream: bid Antibiotic: bid for 2 mos	Both metronidazole cream and antibiotics significantly reduced mean numbers of papules and pustules by >50% within 1 month of treatment (P<0.05).
• Monk, et al ¹⁷	Randomized, double-blind, 0.75% gel vs. 250mg oral oxytetracycline	27	bid for 9 wks	No statistically significant differences found between treatment groups.

Table 1: Some metronidazole studies in the treatment of rosacea.

Drug Interaction

Oral metronidazole may potentiate the anticoagulant effect of coumarin and warfarin, resulting in prolongation of prothrombin time.^{1,2} However, given that only minimal concentrations of metronidazole are detectable in plasma following topical application, the likelihood of systemic interactions would be less with topical than with oral administration.

Pregnancy and Lactation

Metronidazole is classified in pregnancy category B. Following oral administration, metronidazole is secreted in breast milk.² When applied topically, metronidazole blood levels would be substantially lower than following oral administration. The decision of whether to stop nursing or discontinue application of

drug will depend upon the risk to the infant and the importance of the drug to the nursing mother. Topical metronidazole should be used during pregnancy only if there is a clear need.

Pediatric Use

The safety and effectiveness of topical metronidazole use in pediatric patients has not been established.²

Dosage and Administration

Following the first 3 weeks of therapy, clinical improvement should be noted, with continuing improvement through 9 weeks of treatment.² As soon as an acceptable level of response is obtained, the frequency and duration of therapy should be adjusted according

Continued on page 6

Treatments Of Choice For Bullous Pemphigoid

S.M. Cooper MD and F. Wojnarowska, MD
Department of Dermatology, Oxford Radcliffe Hospital, Oxford, UK

ABSTRACT

Bullous pemphigoid (BP) is the most frequently occurring autoimmune blistering disease in Europe and North America. Although it is primarily a disease of the elderly, children and young adults can also develop it. The aim of treatment is to suppress the clinical signs and symptoms of BP without over-treating the patient, because BP tends to spontaneously remit in most patients within approximately 5 years. Mild or localized disease may respond to super-potent topical corticosteroids alone or in combination with tetracyclines with or without niacinamide. More severe or generalized disease usually requires systemic treatment with prednisolone (dose range from 20-70mg/d). Additional immunosuppressant therapy is necessary for more refractory disease.

Key Words: bullous pemphigoid, autoimmune disease

Clinical Presentation and Diagnosis of Bullous Pemphigoid

BP is a non-scarring blistering disease.^{1,2} Tense blisters may arise on normal appearing skin or on erythematous plaques. Blistering may be widespread or occur in one site, typically a flexural site. The involvement of mucous membranes occurs in approximately half of patients. Occasionally an urticarial or eczematous rash may precede blister formation by months or years.

Diagnosis is made by considering the clinical picture, histology and immunofluorescence results. A typical biopsy of a new blister shows a subepidermal cleft with a mixed dermal inflammatory infiltrate containing many eosinophils. Direct immunofluorescence of perilesional skin reveals linear deposits of IgG and/or C3 (rarely IgA, IgM or IgE), and indirect immunofluorescence of serum or blister fluid demonstrates linear IgG at the basement membrane zone.

Principles of Treatment

There are few randomized, controlled trials of therapy for BP, thus information comes mostly from case series, case reports and clinical experience. There are still many unanswered questions. Clinicians differ in their approach to management. Here, we outline our approach:

BP is self-limiting, usually remitting within 5 years, thus it is important not to overtreat the disease. Many of the drugs for BP are potentially hazardous. Drug interactions and side effects are more frequent in the elderly, so that the treatment may be more dangerous than the disease. We favor the use of the minimum doses of systemic therapy to control the disease, modifying the treatment on an individual basis, taking account of the age and general health of the patient and the extent of the disease. Some will have more aggressive disease and need significant immunosuppression. Once control of BP has been achieved, treatment can be gradually tapered off. In practice, treatment should be reduced whenever the disease has been well controlled for a month. It is not necessary to completely suppress all blister formation. The occurrence of an occasional blister ensures that the patient is not being over treated.

Mechanisms of Treatment

Treatments for bullous pemphigoid comprise three categories: anti-inflammatories, immunosuppressants, and immune-modulators.

Anti-inflammatory drugs, e.g., corticosteroids and antibiotics aim to suppress the inflammatory process. Immunosuppressant drugs aim to suppress the production of circulating pathogenic antibodies and include high dose corticosteroids, azathioprine, methotrexate, ciclosporin and cyclophosphamide. Intravenous immunoglobulin is an immune modulator.

Systemic Steroids

The use of systemic corticosteroids is well established although optimum treatment doses are still a subject of debate. Initial treatment doses should take disease severity into account. In localized or mild disease 20mg/d of prednisolone (0.3 mg/kg/d) is sufficient, and for moderate disease 40mg/d or 0.6mg/kg/d. Higher doses of 50-70mg or 0.75-1.0mg/kg/d are indicated in severe disease. Treatment with more than 30mg of prednisolone (0.75 mg/kg) daily is associated with significant mortality and must be tapered as soon as possible.³ However, more severe disease may take longer to come under control. It is important to consider prevention of osteoporosis when steroid treatment is commenced.

Topical Steroids

Topical superpotent steroids, e.g., clobetasol propionate 0.05% have a role in treating localized and mild-to-moderate generalized disease.⁴ In localized and sometimes in generalized disease this treatment alone may suffice. Topical steroids can be a useful adjunct to systemic treatment in severe disease, aiding control of symptoms.

Antibiotics and Nicotinamide

Antibiotics and niacinamide (nicotinamide) are useful first line treatments that may spare some patients from immunosuppressant therapy.⁵ Tetracyclines (oxytetracycline, minocycline or doxycycline) may be prescribed as sole agents or in combination with niacinamide. In local or mild disease, tetracyclines may provide disease control without resorting to systemic prednisolone. In moderate disease, tetracyclines in combination with prednisolone may have a steroid sparing action. We use minocycline (50-100mg/d) or oxytetracycline (500-1000mg/d) when minocycline-induced pigmentation is a problem. Tetracycline is not suitable in renal impairment and doxycycline and minocycline should be avoided in liver impairment. Erythromycin is another option that may be particularly effective in children.⁶

	Treatment	Dose	Principal side effects and cautions
Mild disease	Topical class I corticosteroid, e.g., clobetasol propionate 0.01%	Application once or twice daily	Cutaneous atrophy with long term use
Moderate disease	Topical class I corticosteroid	Application once or twice daily	
	± Prednisolone	20-40mg/d	Immunosuppression; Osteoporosis
	± Tetracycline	Oxytetracycline 500-1000mg/d	Avoid in children, and in renal impairment
		Minocycline 50-100mg/d	Avoid in children, and in hepatic impairment
	± Niacinamide	Start at 500mg/d, increasing in 500mg increments to 2500mg/d over 1-2 months	Gastrointestinal upset; Hepatic impairment at very high dosage
	± Erythromycin	1000-3000mg/d	Gastric upset
Severe disease	± Dapsone sulphamethoxy-pyridazine	50-200mg/d 250-1500mg/d	Dapsone syndrome; Haemolysis; Methaemoglobinaemia; Stevens-Johnson; Toxic Epidermal Necrolysis; Check for G6PD deficiency in racially predisposed
	Prednisolone	50-70mg/d	
Resistant disease Dosage regimes are not yet fully determined	± Azathioprine	up to 2.5mg/kg/d	Myelosuppression; Hepatotoxicity; Measure TPMT before starting treatment.
	Methotrexate	5-12.5mg/week	Hepatotoxicity
	Ciclosporin	2.5-5mg/kg/d	Hypertension; Renal Impairment
	Plasmapheresis		
	Intravenous Immunoglobulins	0.4mg/kg/d polyvalent immunoglobulin for 5 days	Transmission of infection
	Mycophenolate mofetil	1-2g/d	Gastric upset; Bone marrow suppression
	Cyclophosphamide	1-2mg/kg orally or intravenously	Haemorrhagic cystitis; Leucopaenia

Table 1: Therapies used for various stages of BP.

The combination of tetracycline and niacinamide may confer some additional benefit to tetracycline alone.⁷ Niacinamide is started at 500mg/d and then gradually increased to 1,500-2,500mg/d over several weeks. The principal side effect is gastrointestinal upset, but gradual building of the dose helps tolerance of the drug. It is important that therapy, with any of these agents, is withdrawn gradually, over months, to prevent relapse.

Azathioprine

Azathioprine (up to 2.5mg/kg/d) in combination with systemic steroids has a steroid sparing effect, but is associated with increased morbidity and mortality.⁸ Prior measurement of thiopurine methyltransferase activity identifies those at greater risk of developing myelosuppression and also those in whom larger doses may be necessary. We only use azathioprine when response to prednisolone is inadequate.

Dapsone and Sulfonamides

The role of dapsone⁹ and sulfonamides is unclear, however they may have a role in BP unresponsive to first line agents. Glucose-6-phosphate dehydrogenase deficiency should be excluded in at-risk racial groups. There is an increased likelihood of side effects in the elderly.

Other Treatments

Experience with cyclophosphamide, methotrexate, ciclosporin, mycophenolate mofetil and chlorambucil is very limited. Cyclophosphamide treated patients have a high mortality so this treatment is only appropriate in very refractory disease. Methotrexate may be especially useful if there is coexistent psoriasis. The role of ciclosporin and mycophenolate mofetil is undetermined, as no large series have been reported. Intravenous immunoglobulins can give dramatic but transient relief of symptoms

but appear to have no long-term benefits.¹⁰ Plasmapheresis (plasma exchange) may have a role in refractory disease.

Conclusion

It is important that patients with bullous pemphigoid are followed regularly while being treated. Treatment must be regularly reviewed and attempts made to reduce, and ultimately withdraw all treatment if possible. We usually attempt to reduce treatment every 1-2 months if the disease is well controlled. While blistering in most patients is easily controlled, a few patients have very resistant disease, which is therapeutically challenging.

References

1. Wojnarowska F, Eady RAJ and Burge SM. Bullous eruptions. In: Champion RH, Burton JL, Ebling FJG, Eds. *Textbook of Dermatology 6th Edition*, Oxford:Blackwell pp. 1817-98 (1998).
2. Korman NJ. Bullous pemphigoid. The latest in diagnosis, prognosis and therapy. *Arch Dermatol* 134 (9):1137-41 (1998 Sep).
3. Morel P, Guillaume J-C. [Treatment of bullous pemphigoid with prednisolone only: 0.75mg/kg/day versus 1.25mg/kg/day. A multicenter randomized study]. *Ann Dermatol Venerol* 111(10):925-8 (1984) [article in French].

4. Zimmermann R, Faure M, Claudy A. [Prospective study of treatment of bullous pemphigoid by a class I topical corticosteroid]. *Ann Dermatol Venerol* 126(1):13-6 (1999 Jan) [article in French].
5. Hornschuh B, Hamm H, Wever S, et al. Treatment of 16 patients with bullous pemphigoid with oral tetracycline and niacinamide and topical clobetasol. *J Am Acad Dermatol* 36(1):101-3 (1997 Jan).
6. Altomare G, Capella GL, Fracchiolla C, Frigerio E. Treatment of bullous pemphigoid with erythromycin: a reappraisal. *Eur J Dermatol* 9(7):583-5 (1999 Oct-Nov).
7. Fivenson DP, Breneman DL, Rosen GB, Hersh CS, Cardone S, Mutasim D. Nicotinamide and tetracycline therapy of bullous pemphigoid. *Arch Dermatol* 130(6):753-8 (1994).
8. Guillaume J-C, Vaillant L, Bernard P, et al. Controlled trial of azathioprine and plasma exchange in addition to prednisolone in the treatment of bullous pemphigoid. *Arch Dermatol* 129(9):49-53 (1993 Jan).
9. Bouscarat F, Chosidow O, Picard-Dahan C, et al. Treatment of bullous pemphigoid with dapsone: retrospective study of thirty-six cases. *J Am Acad Dermatol* 34(4):683-4 (1996 Apr).
10. Harman KE, Black MM. High-dose intravenous immune globulin for the treatment of autoimmune blistering diseases: an evaluation of its use in 14 cases. *Br J Dermatol* 140(5):865-74 (1999 May).

Continued from page 3

to the severity of the disease. Periods of remission may be induced following treatment with metronidazole cream, although no optimum duration of therapy has been established for the treatment of rosacea.² Long-term therapy may be required as relapse is common following discontinuation of drug treatment. In clinical studies, topical metronidazole therapy for rosacea has been continued for up to 21 weeks.²

Conclusion

Metronidazole should be used as part of an extensive management program. Medical practitioners must educate rosacea patients about how to recognize and avoid trigger factors that can worsen symptoms and interfere with the success of treatment. Multiple studies have demonstrated the therapeutic benefits of topical metronidazole for this condition; furthermore, the agent also helps to prevent relapse. Topical metronidazole therapy may be as effective as oral tetracycline for treating rosacea.¹⁴⁻¹⁸

Acknowledgement

We wish to thank J.E. Swan for her contribution to this manuscript.

References

1. Metronidazole cream 1% (Noritate™, Dermik). *Physicians' Desk Reference*. Medical Economics Company, Inc., Montvale, NJ, USA. (2000) pp. 954-955.
2. McEvoy GK (Editor). Metronidazole. *AHFS Drug Information 2001*®. Bethesda: American Society of Health-System Pharmacists, Inc., pp. 3389-3395 (2001).
3. Miyachi Y, Imamura S, Niwa Y. Anti-oxidant action of metronidazole: a possible mechanism of action in rosacea. *Br J Dermatol* 114(2):231-4 (1986 Feb).
4. Aronson IK, Rumsfield JA, West DP, Alexander J, Fischer JH, Paloucek FP. Evaluation of topical metronidazole gel in acne rosacea. *Drug Intell Clin Pharm* 21(4):346-51 (1987 Apr).
5. Breneman DL, Stewart D, Hevia O, Drake LA. A double-blind, multicenter clinical trial comparing efficacy of once-daily metronidazole 1 percent cream to vehicle in patients with rosacea. *Cutis* 61(1):44-47 (1998 Jan).

6. Jorizzo JL, Leibold 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* 39(3):502-4 (1998 Sep).
7. Bjerke JR, Nyfors A, Austad J, et al. Metronidazole (Elyzol) 1% cream vs placebo cream in the treatment of rosacea. *Clin Trials* 1989;26:187-194.
8. Bleicher PA, Charles JH, Sober AJ. Topical metronidazole therapy for rosacea. *Arch Dermatol* 123(5):609-14 (1987 May).
9. Lowe NJ, Henderson T, Millikan LE, Smith S, Turk K, Parker F. Topical metronidazole for severe and recalcitrant rosacea: a prospective open trial. *Cutis* 43(3):283-6 (1989 Mar).
10. Leibold MG, Medansky RS, Russo CL, Plott RT. The comparative efficacy of sodium sulfacetamide 10%/sulfur 5% (Sulfacet-R®) lotion and metronidazole 0.75% (MetroGel®) in the treatment of rosacea. *J Geriatr Dermatol* 3(5):183-5 (1995).
11. Metronidazole lotion 0.75% (MetroLotion™). *Physicians' Desk Reference*. Medical Economics Company, Inc., Montvale, NJ, USA, pp. 1106-1107 (2000).
12. 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* 40(6 Pt 1):961-965 (1999 Jun).
13. Tan JK. A new formulation containing sunscreen (SPF 15) and 1% metronidazole (Rosasol® Cream) in the treatment of rosacea. *Skin Therapy Lett* 6(8):1-2 (2001 May).
14. Nielsen PG. A double-blind study of 1% metronidazole cream versus systemic oxytetracycline therapy for rosacea. *Br J Dermatol* 109(1):63-5 (1983 Jul).
15. Veien NK, Christiansen JV, Hjorth N, Schmidt H. Topical metronidazole in the treatment of rosacea. *Cutis* 38(3):209-10 (1986 Sep).
16. Schachter D, Schachter RK, Long B, et al. Comparison of metronidazole 1% cream versus oral tetracycline in patients with rosacea. *Drug Invest* 1991;3(4):220-224.
17. Monk BE, Logan RA, Cook J, et al. Topical metronidazole in the treatment of rosacea. *J Dermatol Treat* 1991;2:91-93.
18. Nielsen PG. The relapse rate for rosacea after treatment with either oral tetracycline or metronidazole cream. *Br J Dermatol* 109(1):122 (1983 Jul).
19. Dahl MV, Katz HI, Krueger GG, et al. Topical metronidazole maintains remissions of rosacea. *Arch Dermatol* 134(6):679-83 (1998 Jun).

Garlic Supplements Can Impede HIV Medication

Investigators from the US National Institutes of Health (NIH) observed that garlic supplements sharply reduce blood levels of the anti-HIV drug saquinavir.*

For the first three days of the study, nine healthy HIV-negative volunteers received doses of saquinavir, a protease inhibitor that is effective at slowing the progression of HIV infection. After three days, they were also given garlic caplets twice daily for 3 weeks. Analysis of blood samples showed a 51% reduction in the average overall levels of saquinavir when compared to baseline levels.

Even after a 10-day "wash-out" period, when the volunteers again used only the protease inhibitor for 3 days, their average saquinavir levels were still approximately 35% lower than baseline.

Exactly how garlic supplements disrupt the uptake of saquinavir is unclear. Garlic has a reputation as a natural cholesterol fighter, which has made it popular with HIV+ patients whose cholesterol levels have risen as a result of their HIV medications. The investigators also suspected a strong possibility of a drug interaction because both garlic and protease inhibitors share the same metabolic pathway.

*Piscitelli SC, Burstein AH, Welton N, Gallicano KD, Falloon J. The effect of garlic supplements on the pharmacokinetics of Saquinavir. *Clin Infect Dis* 34(2):234-8 (2002 Jan).



WE'RE ON THE NET! www.skincareguide.com

Once-Daily, Non-Sedating Antihistamine Clarinex® Now Available in the US

Clarinex® 5 mg. tablets (desloratidine, Schering-Plough) are now available by prescription throughout the US. This nonsedating antihistamine provides 24-hour relief and was approved by the US FDA in December 2001, for the treatment of seasonal allergic rhinitis in adults and children >12 years of age. Schering-Plough also received an approvable letter from the US FDA for this product for the treatment of chronic idiopathic urticaria (CIU), or hives of unknown cause. Clarinex® is similar to Schering-Plough's Claritin®, but is believed to be more effective, faster acting, and have milder side-effects.

In clinical trials, this product provided significantly greater symptom relief than placebo with a low incidence of side effects, which included pharyngitis, dry mouth, somnolence and fatigue. However the incidence rate was similar to that found with the placebo.

Source: Schering-Plough Corporation

Update on Drugs

Class	Name/Company	Approval Dates and Comments
Atopic Dermatitis	Pimecrolimus <i>Elidel</i> [®] Novartis Pharmaceuticals	The US FDA approved this topical immunomodulator in December 2001, for the short-term and intermittent long-term treatment of mild to moderate atopic dermatitis in patients >2 years of age who do not respond well to, or may have side effects with conventional treatments.
Antifungal Agent	Butenafine HCl 1% Cream <i>Lotrimin Ultra</i> [®] Schering-Plough	The US FDA approved this antifungal agent in December 2001, for the nonprescription treatment of superficial dermatophytoses.
Antibacterial Agents	Doxycycline <i>Vibramycin</i> [®] Pfizer	The US FDA approved new labeling in November 2001, for treatment of cutaneous and inhalation anthrax after exposure.
Antipsoriatic Agents	Fluocinolone acetonide <i>Derma-Smooth/FS</i> [®] Hill Dermaceutical	The US FDA approved this topical scalp oil in November 2001, for treatment of psoriasis in patients 2-5 years of age.
Immuno-modulatory Agent	Thalidomide <i>Thalomid</i> [®] Celgene Corporation	The EMEA granted orphan drug status in December 2001, for the treatment of multiple myeloma and erythema nodosum leprosum.
Drug News		
Antibacterial Agent	In a double-blind, placebo-controlled trial, RB Nadelman, et al*, recently found that a single dose of doxycycline when administered within 72 hours after a tick bite, was more effective than placebo in preventing the development of Lyme Disease. * <i>N Engl J Med</i> 345(2):79 (2001 July)	
Cauterizing Agent	Debacterol [®] (Northern Research Laboratories), a topical canker sore treatment that has, until recently, been available only through dentists and other healthcare professionals will soon be available to the general public. Debacterol [®] is the only canker sore treatment available that chemically cauterizes the oral lesion in a single treatment.	
Anti-Acne Agent	Micrologix Biotech recently completed a Phase I placebo-controlled study of their new anti-acne treatment, MBI 594AN. This compound is a synthetic, cationic peptide that acts by damaging the bacterial membrane, which results in the rapid death of the treated bacteria. Results from this study indicate that no resistance developed to MBI 594AN among the strains of <i>P. acnes</i> present in the 36 patients who were treated for 6 weeks. Phase II results are anticipated soon.	
HIV/AIDS	A pilot study at the National Institute of Allergy and Infections Diseases suggests that certain people with HIV disease may be able to move from a continuous regimen of anti-HIV therapy to a strategy in which they discontinue and then resume their anti-HIV treatment in a pre-planned, cyclic manner. The approach is known as "structured intermittent therapy". After the study, patients found that there was no deleterious effects on the course of their disease, and as well, noted a significant reduction in drug related side-effects. The investigators also found significant reductions in serum cholesterol and triglyceride levels. Further randomized, controlled clinical trials are currently underway.	

Skin Therapy Letter[®] (ISSN 1201-5989) Copyright 2001 by SkinCareGuide.com. The Skin Therapy Letter[®] is published 10 times annually by SkinCareGuide.com Ltd, 450 - 688 West Hastings, Vancouver, British Columbia, Canada, V6B 1P1. Publications Editor: Penelope Gray-Allan: 604-633-1926, email: grayallan@skincareguide.com. All rights reserved. Reproduction in whole or in part by any process is strictly forbidden without prior consent of the publisher in writing. While every effort is made to see that no inaccurate or misleading data, opinion or statement appears in the Skin Therapy Letter[®], the Publishers and Editorial Board wish to make it clear that the data and opinions appearing in the articles herein are the responsibility of the contributor. Accordingly, the Publishers, the Editorial Committee and their respective employees, officers and agents accept no liability whatsoever for the consequences of any such inaccurate or misleading data, opinion or statement. While every effort is made to ensure that drug doses and other quantities are presented accurately, readers are advised that new methods and techniques involving drug usage, and described herein should only be followed in conjunction with the drug manufacturer's own published literature. Printed on acid free paper effective with Volume 1, Issue 1, 1995.

Subscription Information. Annual subscription: Canadian \$95 individual; \$165 institutional (plus GST); US \$65 individual; \$115 institutional. Outside North America: US\$85 individual; \$135 institutional. We sell reprints in bulk (100 copies of the same article or more). For individual reprints, we sell photocopies of the articles. The cost is \$20 to fax and \$15 to mail. Prepayment is required. Student rates available upon request. Director of Sales: Eileen Larkin: 604-833-9437, email: elarkin@skincareguide.com. Fax: 604-633-1921.