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
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. The reduction in erythema scores at week 9 on the metronidazole side was significantly different from scores on the placebo side (P=0.0006). Another clinical trial studied 19 patients with severe or recalcitrant rosacea. 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 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/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). A 12-week clinical study was conducted in 125 patients with moderate-to-severe rosacea comparing metronidazole 0.75% lotion to its vehicle. 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.

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

In a single-center, double-blind, randomized, contralateral, split-face study, the efficacy and safety of topical metronidazole 0.75% cream was compared to sunscreen vehicle in 120 patients with moderate-to-severe rosacea. After 12 weeks, lesion counts for the Rosasol® group were reduced 70% compared to 23% in the placebo group (P=0.005). 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).

### 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). 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. 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.

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). 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.

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. 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. 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. 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. 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. Dermatotoxicity tests have shown no evidence of contact sensitivity, phototoxicity, or photocontact allergenic reactions.
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 the 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

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

<table>
<thead>
<tr>
<th>Product/Investigator</th>
<th>Study</th>
<th>n</th>
<th>App.</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metronidazole 1%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cream: Noritate® (Dermik) • Breneman, et al5</td>
<td>Multicenter, double-blind, randomized, parallel, 1% cream vs. placebo</td>
<td>139</td>
<td>qd for 10 wks</td>
<td>Overall rosacea severity score significantly greater for 1% metronidazole cream group.</td>
</tr>
<tr>
<td>• Jorizzo, et al6</td>
<td>Multicenter, double-blind, randomized, parallel, 1% cream once daily vs. 1% cream twice daily vs. placebo</td>
<td>277</td>
<td>qd or bid for 10 wks</td>
<td>Using Physician’s Global Assessment Scores the metronidazole qd group rated fair/better improvement (79%) vs. baseline (p&lt;0.01).</td>
</tr>
<tr>
<td>• Bjerke, et al7</td>
<td>Multicenter, double-blind, randomized, 1% cream vs. placebo</td>
<td>97</td>
<td>bid for 8 wks</td>
<td>Statistically significant difference between regimens for reducing papules plus pustules, erythema, overall assessment.</td>
</tr>
<tr>
<td>MetroGel® (Galderma): • Bleicher, et al8</td>
<td>Double-blind, randomized, split-face, paired comparison trial, 0.75% gel vs. vehicle</td>
<td>38</td>
<td>bid for 9 wks</td>
<td>Erythema significantly lower than at baseline and significantly different from placebo group (P=0.006).</td>
</tr>
<tr>
<td>• Lebwohl, et al10</td>
<td>Controlled, randomized, investigator-blinded, 0.75% gel vs. sodium sulfacetamide 10%/sulfur 5% lotion</td>
<td>55</td>
<td>bid for 8 wks</td>
<td>Physician’s Global Assessment Scores indicated consistently greater improvement in the sodium sulfacetamide/sulfur treatment group.</td>
</tr>
<tr>
<td>Rosasol® (Stiefel) • Tan13</td>
<td>Multi-center, randomized, double-blind, 1% metronidazole + sunscreen vs. sunscreen vehicle</td>
<td>120</td>
<td>bid for 12 wks</td>
<td>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).</td>
</tr>
<tr>
<td>Metronidazole vs Oral antibiotics: • Nielsen14</td>
<td>Randomized, double-blind, 1% cream vs. 250mg oral oxytetracycline</td>
<td>48</td>
<td>1% cream: qd Antibiotic: bid for 2 mos</td>
<td>90% of patients showed improvement. No significant difference between 1% cream and oral antibiotics.</td>
</tr>
<tr>
<td>• Veien, et al15</td>
<td>Randomized, double-blind, 1% cream vs. 250mg oral tetracycline</td>
<td>75</td>
<td>bid for 8 wks</td>
<td>No statistically significant differences found between the two groups.</td>
</tr>
<tr>
<td>• Schachter, et al16</td>
<td>Multicenter, randomized, double-blind, 1% cream vs. 250mg oral tetracycline vs. vehicle</td>
<td>101</td>
<td>1% cream: bid Antibiotic: bid for 2 mos</td>
<td>Both metronidazole cream and antibiotics significantly reduced mean numbers of papules and pustules by &gt;50% within 1 month of treatment (P&lt;0.05).</td>
</tr>
<tr>
<td>• Monk, et al17</td>
<td>Randomized, double-blind, 0.75% gel vs. 250mg oral oxytetracycline</td>
<td>27</td>
<td>bid for 9 wks</td>
<td>No statistically significant differences found between treatment groups.</td>
</tr>
</tbody>
</table>

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

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. 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. 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. 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 doxycycline (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.
The combination of tetracycline and niacinamide may confer some additional benefit to tetracycline alone. 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. 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 dapsone 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.\textsuperscript{10} Plasmapheresis (plasma exchange) may have a role in refractory disease.

\textbf{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.

\textbf{References}


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 Venereol 111(10):925-8 (1984) [article in French].


\textit{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.\textsuperscript{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.\textsuperscript{2}

\textbf{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.\textsuperscript{14-18}

\textbf{Acknowledgement}

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

\textbf{References}

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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.


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 non-sedating 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

| Atopic Dermatitis | Pimecrolimus<br/>Elidel®<br/>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<br/>Lotrimin Ultra®<br/>Schering-Plough | The US FDA approved this antifungal agent in December 2001, for the nonprescription treatment of superficial dermatophytoses. |
| Antibacterial Agents | Doxycycline<br/>Vibramycin®<br/>Pfizer | The US FDA approved new labeling in November 2001, for treatment of cutaneous and inhalation anthrax after exposure. |
| Immuno-modulatory Agent | Thalidomide<br/>Thalidomid®<br/>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.


**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 *P. acnes* 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.