Antibiotic Resistance in Acne Treatment

Shannon Humphrey, MD, FRCPC, FAAD
Department of Dermatology and Skin Science, University of British Columbia, Vancouver, BC, Canada

ABSTRACT

Propionibacterium acnes (P. acnes) is an anaerobic bacteria implicated in the pathogenesis of acne. The last 30 years have witnessed an alarming increase in resistance to antibiotics commonly employed to treat acne. Antibiotic resistance in acne represents a significant international public health concern because resistance can occur in more pathogenic bacteria than P. acnes, and an increase in pathogenic P. acnes has been reported. Current treatment guidelines offer strategies to limit the potential for resistance while achieving optimal outcome in the management of inflammatory and non-inflammatory acne.

Key words: acne vulgaris, antibacterial agents, antibiotic resistance, benzoyl peroxide, topical combination therapy

Antibiotic Resistance in Acne Therapy

Propionibacterium acnes (P. acnes) is an anaerobic bacteria implicated in the pathogenesis of acne vulgaris. There are four primary pathogenic factors: excess sebum production, bacterial colonization, inflammation, and abnormal keratinization. Treatment targets as many pathogenic factors as possible and may include a combination of topical and systemic agents.

Although current acne guidelines discourage the use of antibiotics as prolonged monotherapy, about 5 million prescriptions for oral antibiotics are written each year for the treatment of acne. Antibiotics demonstrate anti-inflammatory and antimicrobial effects and work on two levels: to decrease the presence of P. acnes – a resident of the normal microflora found in abnormally high numbers in the sebaceous follicles of patients with acne and a primary factor in the development of inflammatory acne – and to inhibit the production of P. acnes-associated inflammatory mediators. Indeed, topical and oral antibiotics have been the mainstay of acne treatment for over 50 years.

In 1976, there was no evidence of antibiotic-resistant propionibacteria on the skin of over 1000 patients with acne. By 1979, Crawford and colleagues had detected the first indication of resistance to topical erythromycin and clindamycin, which was followed by the emergence of tetracycline-resistant P. acnes in the early eighties. Since then, the incidence of antibiotic resistance in acne has continued to rise across the globe, from 20% in 1978 to 72.5% in 1995, with combined resistance to erythromycin and clindamycin more prevalent than resistance to tetracycline. Evidence suggests that it is the use of topical erythromycin and clindamycin – the most commonly used topical antibiotics in acne – that has contributed to the gradual increase in resistance over the last 20 years. In fact, resistant P. acnes strains have been shown to emerge after only 8 weeks of topical antibiotic monotherapy, with the number of resistant strains increasing progressively over subsequent weeks.

Evidence of Clinical Relevance

Acne does not represent a typical bacterial infection, in which antibiotic resistance directly correlates to treatment failure, because antibiotics demonstrate both antibacterial and anti-inflammatory effects, and P. acnes – existing in the microaerophilic or anaerobic and lipid-rich environment of the pilosebaceous follicle – cannot easily be cultured. However, it is logical to assume that resistance manifests with a reduced clinical response, and this theory is substantiated by the results of several investigations linking resistant strains to higher counts of P. acnes and therapeutic failure. A systematic review of 50 clinical trials using topical antibiotics between 1974 and 2003 paints a startling picture: a significant decrease in the efficacy of topical erythromycin on inflammatory and non-inflammatory lesions over time (Figure 1).

The question remains: what does it matter? While it is true that the prevalence of life-threatening infections caused by P. acnes has greatly increased in the last twenty-odd years, most often in the post-surgical setting in patients with significant medical comorbidities, acute propionibacterial infections are never treated with acne medication. Furthermore, it would seem that antibiotic-resistant acne puts neither patients nor the community at risk for resistant propionibacterial infections.

Resistance in Pathogenic Organisms

Prolonged regimens using either topical or oral antibiotics for the treatment of acne have resulted in selection pressure or the transfer of resistant genes to potentially pathogenic bacteria, such as certain strains of staphylococci or streptococci, and it is these resistant organisms that could present clinical challenges.
The implications are potentially serious. *S. epidermidis* has been found to be pathogenic in certain patients, predominantly those with indwelling catheters, surgical patients, or premature infants.\(^{23-25}\) More ominously, CNS has been shown to transfer resistance to the more pathogenic *S. aureus*,\(^{26}\) which tends to thrive and disseminate more widely in conjunction with topical antibiotic therapy. In a 24-week randomized trial of 2% erythromycin gel versus its vehicle, antibiotic therapy led to an increase from 15% to 40% in erythromycin-resistant *S. aureus* carriage rates in the nose, and resistance increased significantly and substantially in the treated group versus patients receiving vehicle (63% vs. 37%) by the end of the treatment period.\(^{22}\)

For all the potentially pathogenic organisms that develop resistance to anti-acne antibiotics, the question remains: does it really matter? Physicians are unlikely to treat *S. epidermidis* or group A streptococcus with acne medication. However, consider this: first-line systemic agents for community-acquired methicillin-resistant *S. aureus* (MRSA) include minocycline and trimethoprim-sulfamethoxazole, both of which are used for the treatment of acne. Thus far, resistance to minocycline is not common; the same cannot be said about trimethoprim.\(^{27}\) As multi-drug-resistant organisms emerge, therapeutic options continue to shrink.

### Antibiotic Resistance in Acne Treatment: Evidence of Clinical Relevance

- Reduced clinical response to antibiotic therapy
- Potential increase in pathogenicity of *P. acnes*
- Transfer of resistance to more pathogenic organisms

### Strategies to Limit Resistance

Since prescribing practice patterns directly influence the rates of *P. acnes* resistance in the population (i.e., the levels of resistance correlate to the levels of antibiotic use), and since selection pressure may affect more pathogenic bacteria than *P. acnes*, it makes sense to implement strategies and guidelines to limit antibiotic resistance.\(^1\) The Global Alliance to Improve Outcomes in Acne guidelines recommend the combination of a topical retinoid plus an antimicrobial agent as first-line therapy for most patients with acne.\(^1\) When antibiotics are indicated, the guidelines recommend strategies to limit resistance, including the use of oral antibiotics only in moderate and moderately severe cases of acne, and the necessary addition of benzoyl peroxide (BPO) and a topical retinoid to regimens using topical antibiotics in mild-to-moderate cases.

### Strategies to Limit Antibiotic Resistance in Acne

- Avoid topical or oral antibiotics as monotherapy or maintenance therapy
- Limit duration of antibiotic use and assess response at 6 to 12 weeks
- Use concomitant BPO (leave-on or wash)
- Avoid simultaneous use of oral and topical antibiotics without BPO
- Use topical retinoid +/- BPO as maintenance in lieu of antibiotics

Evidence suggests that BPO, alone or in combination with a topical retinoid, may serve as an effective and well tolerated option for treating acne in patients with resistant *P. acnes*, while minimizing the development of further antibiotic resistance. Topical retinoids exhibit both anti-inflammatory and antimcomedonal activities\(^{11}\) and are highly effective in reducing both inflammatory and non-

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**Figure 1:** Impact on acne: efficacy of topical erythromycin over time (empty circles: studies evaluating treatment efficacy after 8 weeks; asterisks: studies evaluating treatment efficacy after 12 weeks).

Figure from Simonart T, Dramaix M., Treatment of acne with topical antibiotics: lessons from clinical studies. *Br J Dermatol.* 2005 Aug;153(2):page 399, Figure 1. Reprinted with permission from John Wiley and Sons.

Levy and colleagues investigated the effects of topical and/or oral antibiotics on the oropharyngeal flora in patients with acne.\(^{19}\) Patients treated with any antibiotic exhibited a 3-fold greater risk of group A streptococcus colonization by Streptococcus pyogenes (*S. pyogenes*) compared to patients not using antibiotic therapy. Eighty-five percent of *S. pyogenes* cultures from those using antibiotics were resistant to at least one tetracycline antibiotic, compared to 20% from those not using antibiotics.

A subgroup analysis of topical versus oral antibiotics found similar prevalence rates, indicating that topical antibiotics have an impact on distant flora and resistance patterns by direct inoculation or systemic absorption. Like their oral counterparts, topical antibiotics may alter the microbial equilibrium through selective elimination of certain bacteria, allowing species like *S. pyogenes*, which would normally be held in check, to flourish.\(^{19}\)

Studies have clearly demonstrated that the use of topical erythromycin increases counts of resistant coagulase-negative staphylococci (CNS) on both local and distant anatomical sites.\(^{20-22}\) Harkaway and colleagues demonstrated aerobic flora dominated by *Staphylococcus epidermidis* (*S. epidermidis*) completely resistant to erythromycin and partially resistant to clindamycin and tetracycline after 12 weeks of treatment.\(^{20}\) Vowels and colleagues found that the prevalence and density of resistant organisms persisted and did not return to baseline values until 6 weeks after discontinuation of topical antibiotic therapy.\(^{21}\)

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**Figure 1:** Impact on acne: efficacy of topical erythromycin over time (empty circles: studies evaluating treatment efficacy after 8 weeks; asterisks: studies evaluating treatment efficacy after 12 weeks).

Figure from Simonart T, Dramaix M., Treatment of acne with topical antibiotics: lessons from clinical studies. *Br J Dermatol.* 2005 Aug;153(2):page 399, Figure 1. Reprinted with permission from John Wiley and Sons.
inflammatory lesions. BPO is a broad-spectrum antibacterial agent that comes in many formulations and works through the interaction of oxidized intermediates with various constituents of microbial cells. Despite its widespread use, bacterial resistance has not been reported.

Leave-on products containing BPO not only suppress existing insensitive strains, but also reduce the emergence of erythromycin- and clindamycin-resistant strains during antibiotic therapy. Moreover, the concomitant use of BPO with a topical antibiotic is highly effective in reducing the colony counts of cutaneous P. acnes. Even simple washes containing BPO effectively reduce P. acnes, including resistant populations. Leyden and colleagues assessed the effectiveness of a gel combination treatment containing 0.1% adapalene and 2.5% BPO in healthy patients with high P. acnes populations resistant to erythromycin, tetracycline and clindamycin, and found a significant reduction in resistant strains by week 4. Indeed, therapy with a combination of adapalene and BPO eradicated some resistant strains entirely in some patients.

Subantimicrobial Dosing
There is some evidence that subantimicrobial doses of antibiotics may reduce inflammation and provide immunomodulatory effects without risk of any resistance. Doxycycline is a second-generation tetracycline class antibiotic normally used at a dose of 100 mg to 200 mg/day in the treatment of acne. Skidmore randomized 51 patients with moderate acne to twice daily 20 mg doses of doxycycline or placebo for 6 months. Active treatment significantly reduced the number of inflammatory and non-inflammatory lesions by more than 50% and led to a greater overall improvement compared to placebo, with no change in number or severity of resistant pathogens or evidence of antimicrobial effect on the skin flora. Toossi and colleagues compared subantimicrobial doses (20 mg twice daily) with antimicrobial doses (100 mg daily) in a prospective, double-blind, randomized controlled trial of 100 patients with moderate facial acne. Both treatments significantly decreased inflammatory lesion counts; subantimicrobial dosing led to an 84% and 90% reduction in the number of papules and pustules, respectively. Although more rigorous trials designed to study the impact on follicular and cutaneous microflora and resistance patterns are warranted, these early results are promising and may represent a future possibility for the management of acne vulgaris.

Conclusion
Although antibiotics play an important role in acne management, the increase in P. acnes resistance should be cause for concern and serve as the impetus for change in prescribing patterns and treatment algorithms. Not only are resistant strains linked to lack or worsening of clinical response to treatment, but the pathogenicity of P. acnes has increased over recent years, and most importantly prolonged regimens of antibiotic therapy have led to the transfer of resistance among non-targeted pathogenic bacteria. Limiting the frequency and duration of antibiotic use and adding the topical antimicrobial agent BPO will minimize the development of resistance while maintaining efficacy in the treatment of inflammatory and non-inflammatory acne lesions.

References
Device-Based Therapies for Onychomycosis Treatment
Aditya K. Gupta, MD, PhD, MBA, FAAD, FRCP:1,2 and Fiona Simpson, HBSc2
1Division of Dermatology, Department of Medicine, University of Toronto, Toronto, ON, Canada
2Mediprobe Research Inc., London, ON, Canada

ABSTRACT
Device-based therapies are promising alternatives for the treatment of onychomycosis because they can mitigate some of the negative factors associated with treatment failure. There are four categories of device-based treatments: laser devices, photodynamic therapy, iontophoresis, and ultrasound. These therapeutic modalities are noninvasive procedures that are carried out by medical professionals, reduce the need for long-term patient adherence, and avoid adverse reactions associated with conventional systemic antifungal therapies.

Key words: antifungal, iontophoresis, laser devices, nails, onychomycosis, photodynamic therapy, ultrasound

Introduction
Onychomycosis is a common nail disorder that faces significant barriers to successful treatment. Etiologically, fungal pathogens such as dermatophyte fungi, yeasts, and non-dermatophyte molds invade and colonize the nail plate, bed, and matrix creating an entrenched infection.1-10 The prevalence of onychomycosis is estimated at 2-8% of the global population. A number of medical conditions can also confer an increased risk of co-morbid onychomycosis infection including diabetes,11 peripheral vascular disease,11 HIV,11 immunosuppression,13,14 obesity,15 smoking,11 and increased age.14 Many individuals have sustained infections persisting for months or years and, hence, they may not be motivated to initiate or complete therapy due to a perception that their condition is untreatable.

Onychomycosis has traditionally been treated by oral and topical antifungals16 that often yield low to moderate efficacy. Even when pharmacotherapy initially results in a mycological cure, the relapse and/or reinfection rate ranges between 16-25%,17,18 Successful treatment for onychomycosis requires antifungal drugs to penetrate the nail plate and nail bed, but incomplete dissemination to the lesion is a problem for both oral and topical agents. Antifungal drugs may be associated with adverse effects that can cause patients to discontinue treatment and therapy may be complicated with the presence of a co-morbid condition.19,20 Additionally, the extended course of treatment may discourage patient compliance, which poses a significant detriment to effective therapy. Thus, these factors can contribute to the suboptimal delivery of conventional therapy for onychomycosis.

Device-based therapies are promising solutions for the treatment of onychomycosis because they can mitigate some of the negative factors that contribute to treatment failure. There are four categories of device-based treatments: laser devices, photodynamic therapy, iontophoresis and ultrasound. Each of these techniques is a noninvasive procedure conducted by a medical professional, which reduces the need for long-term patient compliance. Photodynamic therapy, iontophoresis and ultrasound are used in combination with local pharmacological agents, thereby avoiding adverse effects associated with systemic antifungal therapy.

Laser Therapy
Laser treatment of onychomycosis infections uses the principle of selective photothermolysis.21,22 Laser therapy is intended to exploit the differences in laser energy absorption and thermal conductivity between the fungal infection and the surrounding tissue. The absorption of light energy by the fungi results in the conversion of the energy into heat or mechanical energy.23 Fungi are heat sensitive above 55°C, so absorption of laser energy that results in sustained photothermal heating of the mycelium (10+ minutes) is likely to result in fungicidal effects.23,24 However, heating dermal tissue to temperatures above 40°C results in pain and necrosis; therefore, the laser energy format must either be pulsed to allow the dissipation of heat by the tissue through its superior thermal conduction or delivered at a moderate energetic level to prevent tissue damage. The exact mechanism of laser therapy is still under investigation, but it may combine direct fungicidal effects of the laser with induced modifications in the immune system or changes in the local microenvironment.

Laser therapy for onychomycosis is currently being studied in vitro and in vivo. In addition, at the time of this writing, the following lasers have been granted FDA marketing approval for the treatment of onychomycosis: PinPointe™ FootLaser™ (PinPointe USA, Inc.),25 Cutera GenesisPlus™ (Cutera, Inc.),26 Q-Clear™ (Light Age, Inc.),27 CoolTouch VARIA™ (CoolTouch, Inc.),28 and JOULE ClearSense™ (Sciton, Inc.).29 The parameters of lasers that have been FDA cleared or tested and supported by publications for onychomycosis are summarized in Table 1. It is important to note that regulatory clearance of device systems are made on the basis of “substantial equivalence” to the technical specifications of pre-existing devices approved for marketing for onychomycosis, not on the basis of clinical trials data, so these systems cannot be directly compared to pharmacologic therapies.
Solid State Lasers
Solid state lasers use a solid crystal rod and they include many of the common commercial lasers such as the neodymium-doped yttrium aluminum garnet (Nd:YAG) and titanium sapphire (Ti:Sapphire) lasers. Solid state lasers may be built for use as continuous lasers or as pulsed lasers with pulse durations in the millisecond, microsecond, nanosecond, or femtosecond ranges. The maximum pulse energy increases as the pulse length decreases, so different pulse formats may result in greater non-specific heating of the nail plate, or require longer treatment lengths to produce a fungicidal effect. The lasers that have been approved for the treatment of onychomycosis in North America have all been Nd:YAG lasers.

Long Pulse Laser Systems
Long pulse Nd:YAG lasers have received CE Marking in Europe (the mandatory conformity designation for marketed products in the European Economic Area), but they have not yet been approved to treat onychomycosis in North America. The pulse duration for these lasers is in the millisecond range. These lasers can cause a high degree of non-specific heating and may need to be operated in the presence of a dedicated cooling system. The largest study of millisecond Nd:YAG lasers was conducted using the Fotona Dualis SP™ laser on 162 participants in Serbia. Fungal infections in both fingernails and toenails were identified by potassium hydroxide (KOH) microscopy. Participants were treated with a 30–40 J/cm² energy fluence with a spot size of 4 mm and a pulse duration of 35 ms in the presence of cold air cooling. The nail plate was treated in a spiral pattern. A 2 minute wait period was observed before repeating the laser treatment. Participants received 4 treatments at 1 week intervals and they were followed after therapy from 12-30+ months. A completely clear nail plate was achieved by 93.5% of participants. The Fotona Dynamis™ family of laser systems has the same technical parameters as the laser used in the studies described above and has received marketing clearance in Europe.

Short Pulse Laser Systems
The first two lasers that were sanctioned by the FDA for the treatment of onychomycosis (PinPointe™ FootLaser™ and Cutera GenesisPlus™) both use flashlamp-pumped short pulse Nd:YAG lasers. The CoolTouch VARIA™ laser is the most recent addition to this class of devices. These lasers emit 100–3000 µs pulses with an energy fluence of 25.5 J/cm² for a 1 mm spot size. The PinPointe™ FootLaser™ was used in an initial phase I/II clinical trial. Seventeen participants demonstrating great toenails afflicted with onychomycosis were enrolled and randomized into treated (n=11) or untreated (n=6) groups. Participants received a single treatment and were followed-up at 3 and 6 months. At the 6 month time period, 11 of 14 treated toes showed improvement in clear linear nail growth. Clinicaltrials.gov reports that a phase III clinical trial for the PinPointe™ laser (NCT00935649) was completed on November 29, 2010, but the data from this study remains unpublished. Cutera has released a white paper on the GenesisPlus™ laser that reported a 70% improvement rate in the 7 participants treated.

<table>
<thead>
<tr>
<th>Laser System</th>
<th>Type of Laser</th>
<th>Wavelength (nm)</th>
<th>Energy Fluence (J/cm²)</th>
<th>Spot Size (mm)</th>
<th>Pulse Length</th>
<th>Pulse Frequency (Hz)</th>
<th>International Approvals for Onychomycosis</th>
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Table 1: Laser device systems
(-) = data unavailable; EU = European Union; US = United States
with 2 sessions of laser therapy. The JOULE ClearSense™ laser was tested in an initial trial of 21 patients.³⁶ Onychomycosis was confirmed by culture and periodic-acid schiff (PAS) microscopy. Patients were treated 4 times, at 1 week intervals with a pulse length of 0.3 ms, an energy fluence of 13 J/cm², and a repetition rate of 6 Hz. Follow-up mycological culture was negative in 95% of patients.³⁶ Clinical trials data for the CoolTouch™ laser has not yet been released.

An additional clinical study was published by Hochman et al. using a short pulse Nd:YAG laser system that has not been FDA cleared for onychomycosis.³⁷ This study confirmed active fungal infections in toenails and fingernails by culture or PAS stain. Participants were treated with a 223 J/cm² energy fluence with a 2 mm spot size for ≤45 seconds. Each subject received 2-3 treatments spaced at least 3 weeks apart. Antifungal cream was used daily where anatomically possible during this study. The efficacy of treatment was followed for between 4-6 months after therapy. Treatment resulted in negative mycological culture in 7 of 8 participants.

CoolTouch, Inc. is also conducting a clinical trial with a 1320 nm Nd:YAG laser (NCT01498393).³⁸ The CoolTouch CT3 Plus™ with the CoolBreeze Zoom handpiece can be operated in short pulse (450 μs) or continuous mode.³⁹ The handpiece has a pre-set temperature threshold that employs a cryogen cooling system.⁴⁰ Duration of the trial is 6 months and the inclusion criteria require patients to have a fungal infection on both great toenails.

Q-switched Laser Systems

Q-switched lasers have a pulse duration in the nanosecond range and they emit the highest peak power per pulse of all the Nd:YAG lasers. In vitro, an energy fluence of 4 J/cm² optimally inhibited Trichophyton rubrum (T. rubrum) colony growth.⁴¹ The Light Age Q-Clear™ is a FDA-cleared Q-switched Nd:YAG 1064 nm laser.²⁷ The FDA 510(k) summary for this laser device states that “Light Age, Inc.’s study of 100 randomized subjects of both genders, including Caucasian, Asian, African American, and Latino, has demonstrated substantially effective clearance of dystrophic toenails having a clinically apparent diagnosis of onychomycosis. Statistical analysis of results indicates significant apparent clearing in 95% of the subjects with an average clearance of affected areas of 56 ± 7% at 98% level of confidence.”²⁷

Modelocked Laser Systems

A modelocked femtosecond pulsed Ti:Sapphire laser tuned to 800 nm was used in an in vitro study on T. rubrum.⁴² Nail clippings were obtained from participants with onychomycosis and the fungal infection was confirmed by culture (n=99). The cultures were irradiated with a Ti:Sapphire laser that was pumped by a solid-state laser, which emitted 200 fs pulses at a frequency of 76 MHz through a variety of numerical apertures from 0.12 to 0.45. Treatment with energy above 7x10⁴ photons m² s⁻¹ resulted in a 100% fungicidal effect.

Near Infrared Diode Lasers

Diode lasers use semiconductors for the optical gain medium as an alternative to solid crystals. The diode lasers that are currently under investigation for onychomycosis operate at near infrared wavelengths. The Noveon® laser (Nomir Medical Technologies) is an 870 nm and 930 nm dual wavelength diode laser.⁴³ In vitro studies have shown that 870 nm and 930 nm wavelengths photoinactivate T. rubrum and Candida albicans, and have a minimal negative effect on cultured fibroblasts.⁴⁴ Preliminary trials for the Noveon® laser have been conducted.⁴² Distal and lateral subungual onychomycosis was confirmed by culture or PAS stain and each participant received 4 treatments on days 1, 14, 42 and 120. Each treatment comprised 4 minutes of dual wavelength therapy, followed by 2 minutes of 930 nm treatment. At 180 days, the participants showed an 85% improvement of infection in 26 toes treated.⁴³ The status of the phase II and II/III trials for the Noveon® laser in onychomycosis (NCT00771732 and NCT00776464) remains unknown.⁴⁵,⁴⁶

ConBio Inc. has registered a single assignment, open label clinical trial (NCT01452490) for a near infrared diode laser.⁴⁷ The V-Raser® laser is a 980 nm near infrared diode laser that has previously been marketed for the removal of vascular lesions. The study aims to enroll 50 participants at two podiatric practices in the United States. Participants will receive 4 laser treatments at 6 week intervals.⁴⁷

Photodynamic Therapy

Photodynamic therapy (PDT) uses visible spectrum light to activate a topically applied photosensitizing agent, which generates reactive oxygen species that initiate apoptosis. Photodynamic therapy was originally optimized for actinic keratosis, but photosensitizers can also be absorbed by fungi.⁵⁸,⁴⁹ The effects of various photosensitizing agents have been studied in vitro and in vivo. These include 5-aminolevulinic acid (ALA), methyl aminolevulinate (MAL), and 5,10,15-tris (4-methylpyridiuium)-20-phenyl-[21H,23H]-porphine trichloride (Sylsens B).

Heme Biosynthesis Intermediates - ALA and MAL

ALA and its methyl ester MAL are heme precursors. They cause a build-up of protoporphyrin IX (PpIX), which is a photodynamically active molecule. In the presence of the correct spectrum of light, PpIX generates reactive oxygen species that initiate apoptosis.⁵⁰ Both of these drugs are commercially available for the treatment of actinic keratosis. Several studies have tested these formulations in small studies on participants with onychomycosis (Table 2).⁵¹-⁵⁴ These studies are heterogeneous, preventing any form of direct comparison; however, these investigations have shown promising initial results, but their small sample sizes (n<30) limit our ability to draw conclusions on the efficacy of this mode of therapy. The protocols developed for these studies indicate that the nail plate should be pre-treated with urea ointment to soften the nail plate prior to application of the photosensitizer.

Non-Heme Porphyrins - Sylsens B

Sylsens B is a non-heme porphyrin that has been used for in vitro studies on T. rubrum. PDT with Sylsens B is fungicidal in T. rubrum suspensions of both hyphae and microconidia at concentrations above 10 μM.⁵⁹,⁵⁵,⁵⁶ PDT with Sylsens B is also fungicidal when T. rubrum is adhered to keratinized structures.⁵⁷ In vitro experiments determined that ultraviolet-A (UVA-1) light is fungicidal in commercial strains and clinical isolates of T. rubrum, so it was an ideal excitatory light source for PDT.⁵⁸ The clinically isolated strain required a higher dose of Sylsens B (9 μM) than the commercial strain (1 μM) using a UVA-1 energy fluence of 18 J/cm².⁵⁹ Sylsens B has not yet been tested in vivo.
Table 2: In vivo studies of ALA and MAL PDT

<table>
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<tr>
<th>Study Parameters</th>
<th>Watanabe et al. 2008</th>
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<td>3 hours</td>
<td>3 hours</td>
<td>4 hours</td>
</tr>
<tr>
<td>Irradiation Source</td>
<td>630 nm laser 100 J/cm²</td>
<td>630 nm 36 J/cm²</td>
<td>570-670 nm 40 J/cm²</td>
<td>635 nm 37 J/cm²</td>
</tr>
<tr>
<td>Length of Irradiation</td>
<td>-</td>
<td>7 min 24 sec</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Number of Treatments</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Treatment Interval</td>
<td>N/A</td>
<td>15 days</td>
<td>2 weeks</td>
<td>2 weeks</td>
</tr>
<tr>
<td>Follow-up Period</td>
<td>6 months</td>
<td>24 months</td>
<td>18 months</td>
<td>6 months</td>
</tr>
<tr>
<td>Mycological Cure Rate</td>
<td>100%</td>
<td>100%</td>
<td>43%</td>
<td>100%</td>
</tr>
<tr>
<td>Complete Cure Rate</td>
<td>100%</td>
<td>100%</td>
<td>36.6%</td>
<td>100%</td>
</tr>
</tbody>
</table>

(-) = data unavailable

Iontophoresis

Iontophoresis is a technique that uses a low level electrical current to increase the transport of drugs across semi-permeable barriers. The limitation of many topical treatments for onychomycosis is their inability to fully penetrate the nail plate.\(^6^9\) This technique may be more successful in incorporating the drug into the nail plate and passing it through the plate to ensure that it penetrates the nail bed and matrix. Iontophoresis is currently being optimized for terbinafine, because it has the highest antifungal effect on dermatophytes in vitro.\(^6^9\) There are two iontophoresis devices currently in clinical trials.

Iontophoresis increases the amount of terbinafine accumulated in the nail plate over the uptake from a passive source.\(^6^1\)\(^-\)\(^6^7\) The nail plate then acts as a reservoir of terbinafine that is then released into the nail bed and matrix over 60-70 days.\(^6^2\)\(^-\)\(^6^5\)\(^,\)\(^6^7\) The drug uptake during iontophoresis can be enhanced after removal of the dorsal layer of the nail plate, or in the presence of keratolysis.\(^6^4\) The devices by NB Therapeutics were effective at targeting the nail plate exclusively and both the nail plate and surrounding skin.\(^6^3\) The iontophoretic device (Electrokinetic Transungual System) by Transport Pharmaceuticals was registered in a phase I clinical trial (NCT00768768) that has since been completed, but the data remains unpublished.\(^6^8\) A phase II clinical trial is also ongoing in North America (NCT01484145).\(^6^9\)

The Power Paper iontophoretic patch device was used in a single preliminary trial of 38 participants.\(^6^1\) Infections were confirmed by both KOH examination and mycological culture. The participants were randomized into two groups for the treatment of a single great toenail. The first group received terbinafine iontophoresis with a current density of 100 μA/cm². The second was treated with the terbinafine gel patch without iontophoresis. The participants wore the patch overnight, every day for 4 weeks. After the initial visit, two further iontophoresis treatments were conducted. Follow-up occurred at 8 weeks and 12 weeks. At the final follow-up, 84% of participants demonstrated a mycological cure confirmed by KOH microscopy.

Ultrasound Drug Delivery System

The most recent development in device-based treatments for onychomycosis is an ultrasound mediated nail drug delivery system.\(^7^0\) This system has been tested in a canine nail model. The intent was to determine which period of 1.5 W/cm² ultrasound treatment increased the nail uptake of a blue dye. Findings showed that the 120 second period was the most effective, increasing dye permeability by 1.5 fold. Further studies will be required to determine if this technique is suitable for existing antifungal drugs.

Conclusion

Device-based therapies for onychomycosis show promise in initial clinical studies involving lasers, photodynamic therapy, iontophoresis, and ultrasound-based therapy. Device-based treatments may be advantageous because they are conducted in the clinic and only require short-term patient compliance. These modalities also have the potential to reduce adverse events caused by antifungal drugs, as they are highly localized treatments. Devices may also be alternatives for patients whose susceptibility to onychomycosis infection arises from a co-morbidity, as these therapies do not interact with the drugs involved in the management of such conditions.\(^6^5\)\(^,\)\(^6^6\) In order to substantiate the efficacy of device-based therapies for onychomycosis, randomized
controlled trials with mycological evaluation and long-term follow-up are required. We believe this therapeutic area will continue to expand and hope that broader clinical investigations will result in new options for practitioners.

References


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**Antibiotic Resistance in Acne Treatment - references continued from page 3**


Apremilast (CC-10004), an orally administered phosphodiesterase-4 inhibitor, has been under active investigation for the treatment of psoriasis, psoriatic arthritis (PsA) and other chronic inflammatory diseases. Apremilast appears to dose-dependently inhibit tumor necrosis factor-alpha (TNF-α) production. In September 2012, a press release by Celgene International reported that three pivotal phase III, randomized, placebo-controlled studies (PALACE-1, 2 & 3) including approximately 1,500 patients, achieved statistical significance and clinically meaningful improvements for the primary endpoint, as well as other measures of signs and symptoms and physical function for patients receiving apremilast 20 mg or 30 mg twice-daily. Among PsA patients, statistically significant response of ACR20 (a measure of success in reducing symptoms) was shown at week 16, which was maintained through week 24. Studies are ongoing through to week 52. Based on the combined PALACE-1, 2 & 3 studies for PsA, a new drug application (NDA) is expected to be filed with the FDA in the first quarter of 2013. A combined marketing authorization application (MAA) submission for PsA and moderate to severe psoriasis in Europe is also planned for the second half of 2013.

More information is available at:
http://ir.celgene.com/phoenix.zhtml?c=111960&p=irol-newsArticle&ID=1732178&highlight=