Volume 19 Number 9
September 2013

Review

Lasers and photodynamic therapy in the treatment of onychomycosis: a review of the literature.

Caitlin Becker BS[1], Andrea Bershow MD[1,2]

Dermatology Online Journal 19 (19): 1

[1]University of Minnesota, [2]VA Medical Center Minneapolis

Correspondence:

Dr. Andrea Bershow
VA Medical Center, Minneapolis
Department of Dermatology
One Veterans Drive, Minneapolis, MN 55417
andrea.bershow@va.gov

Abstract

Onychomycosis is a widespread problem. Oral antifungal medications are currently the gold standard of care, but treatment failure is common and oral therapy is contraindicated in many cases. There is a need for effective treatment without the systemic complications posed by oral therapy. Laser and photodynamic therapy may have the potential to treat onychomycosis locally without adverse systemic effects; some small studies have even reported achieving clinical and mycologic cure. However, there is reason for restraint; these therapies are expensive and time-consuming. Furthermore, they may not be covered by insurance and have not been proven effective with randomized, controlled clinical trials. This paper will review current literature regarding the use of laser and photodynamic therapy as potential treatments for onychomycosis.

Keywords: Onychomycosis, laser, photodynamic therapy

Introduction

Onychomycosis is a common problem involving chronic fungal infection of the nail, which can result in nail dystrophy and discomfort. Most of these cases are caused by dermatophytes, with *Trichophyton rubrum* implicated in the majority of cases [1]. The prevalence of onychomycosis in Canada and the UK is estimated to be around 10% with elderly, diabetic, and chronically immunosuppressed patients disproportionately affected [1,2]. The overall health consequences of onychomycosis can be substantial. Compared with unaffected, age-matched peers, patients with onychomycosis report poorer general health, mental health, and emotional well-being; patients also note more pain. Additionally, onychomycosis can have a significant negative impact on a patient's occupation if it involves standing or walking for long periods [3,4]. In the diabetic population, dystrophic toenails caused by chronic fungal infection can injure the surrounding tissue, possibly increasing the risk of diabetic ulcers, which can eventually lead to amputation [5].

Oral Therapy

Several oral therapies are available to treat onychomycosis. Terbinafine is more efficacious than other oral agents such as itraconazole, griseofulvin, or fluconazole and is therefore considered first-line treatment [6]. However, terbinafine is contraindicated in certain patient populations, including patients with liver disease. Meta-analysis of randomized controlled trials reveals an average cure rate of only 65.6% after 3 months of therapy with terbinafine [7,8]. Itraconazole is a CYP3A4 inhibitor and may cause adverse events in patients taking HMG-CoA reductase inhibitors, oral hypoglycemic agents, and some benzodiazepines [9]. Many patients are ineligible for oral therapy owing to polypharmacy and comorbidities. There is a need for efficacious therapy that does not cause systemic side effects and lacks multiple drug-drug interactions.

Laser Therapy

Carbon dioxide (CO_2) lasers have been used in the past to treat onychomycosis, and were described as "effective but unpredictable" [10]. And whereas CO_2 laser is generally not used for the treatment of onychomycosis, the utility of other lasers is being studied. One of the most appealing characteristics of laser therapy is its ability to selectively deliver energy to the target tissue and avoid systemic side effects. Mammals are more resilient than mycotic organisms to the effects of laser treatment [11]. Although mammalian cells are also affected by changes in membrane permeability and reactive oxygen species (ROS) generation, these changes are more transient than those in fungal cells [11]. Only 15% of mammalian cell viability was lost when mouse fibroblasts were subjected to treatment with an 870/930nm laser at 13 times the lethal dose for fungi [11]. After porcine skin was treated with an 870/930nm blended laser, all erythema, collagen degeneration, and monocellular infiltrate subsided completely within 72 hours [11]. In addition, scanning electron microscopy has shown that the underside of the nail plate can be effectively treated at one order of magnitude below the damage threshold of the nail matrix, implying that lasers may safely be used to treat fungus while maintaining a low risk for nail dystrophy [12]. However, care must be taken with laser therapy because frequent exposure to near infrared wavelengths can accelerate photoaging and decrease Type 1 collagen. Nd:YAG lasers have been shown to ablate healthy tissues by excessive heating through "pulse stacking", when overlapping of pulses results in a higher delivered dose [13]. Using good technique to alter energy distribution may help prevent tissue damage caused by pulse stacking [13].

In Vitro Studies

The fungicidal action of lasers is accomplished through direct thermal effects and possibly via the generation of reactive oxygen species [14]. Bornstein *et al* achieved 100% inactivation of *Trichophyton rubrum in vitro* 91 hours after treatment with an 870/930nm dual wavelength laser, whereas *Candida* was completely inactivated at 20 hours [11]. Manevitch *et al* irradiated *T. rubrum*-infected nail clippings with an 870nm infrared titanium sapphire laser pumped by a solid state laser. Using intensities of at least 7×10^{31} photons/m^2s produced negative cultures 4 weeks post-irradiation [12]. Another *in vitro* study compared the ability of various wavelengths of light to inhibit fungal growth. Treating *T. rubrum* colonies with 695 nm to 1,000 nm intense pulsed light , 585nm pulsed dye, 2940 nm Er:YAG, or 532nm KTP lasers did not inhibit their growth [15]. However, colonies treated with Q-switched 532nm and 1064nm Nd:YAG lasers had a significantly lower growth rate [15]. The efficacy of the 532 nm wavelength may relate to absorption by the red pigment xanthomegnin, which is present in high concentration in *T. rubrum* [15,16]. These studies demonstrate that some lasers have the potential to inhibit fungal growth without the use of a photosensitizing agent.

In Vivo Studies

Several authors have reported similar success using lasers *in vivo*. In one study, seven patients (all culture positive for *Trichophyton, Phaeoannellomyces,* or *Rhodotorula)* received four treatments with an 870/930 nm blended laser at days 1, 7, 14, and 60 [11]. At day 60, all patients tested negative for fungus on nail biopsy and culture and no adverse effects were reported [11]. Another study, funded by Nomir Medical Technologies, utilized the same protocol as the previous study [17]. An independent panel assessed photographs from before and 180 days after treatment and determined that 20 of the 26 the treated toenails (77%) exhibited improvement from baseline, 10 (39%) toenails were culture negative and showed at least 3mm of clear growth, and 3/5 patients infected with *Candida* were culture negative by the second treatment [17]. Of note, daily topical, non-prescription antifungal treatment was used after the second treatment in both studies, which may have improved clinical and mycologic clearance rates [11,17].

Three studies achieved clinical success using a 1064nm Nd:YAG laser. One study treated a total of 194 infected nails in 72 patients with a 1064 nm Nd:YAG laser [18]. Patients with especially thickened nails applied 40% compounded urea under occlusion for 3 nights; all patients then received four laser treatments with one week between sessions [18]. Three months post-treatment, 95.8% of the treated patients were clinically clear and culture negative [18]. The three patients who remained infected at three months were treated again at that time. All patients were observed for recurrence at 6, 9, and 12 months. At the end of the study all 72 patients enrolled were clinically and culture negative [18]. A study by Hochman achieved similar success with a 1064nm pulsed Nd:YAG laser [19]. Eight patients were treated every three weeks for three sessions [19]. In this study seven out of eight patients with confirmed fungal infection were culture negative after the third treatment session with no reports of significant side effects [19]. These patients were also prescribed topical antifungal therapy after the first laser treatment [19]. A third study by Kimura *et al* treated 37 toenails with microscopically confirmed onychomycosis up to three times with a 1064nm Nd:YAG laser [20]. At follow up 16 weeks later, 81% of toenails exhibited moderate to complete clearance whereas 51% were completely clear and culture negative [20]. These studies suggest that there may be a role in using Nd:YAG lasers in treating onychomycosis, but further trials are needed.

Photodynamic Therapy

Photodynamic therapy (PDT) is another therapy being investigated for use in treatment of onychomycosis. PDT uses visible light to excite photosensitizing agents, which results in the formation of ROS, producing selective tissue destruction. Aminolevulinic

acid (ALA), and methyl-aminolevulinic acid (MAL), are hydrophilic porphyrin precursors that saturate the normal heme pathway and yield the photosensitizer protoprophyrin IX (PpIX). PpIX is an effective inhibitor of *Trichophyton rubrum* when used in conjunction with red-spectrum light [21]. *Trichophyton rubrum* incubated *in vitro* for one hour with the porphyrin compound Sylsens B, and exposed to a red lamp, showed total destruction of fungal hyphae and spore inactivation with no growth 3 months after treatment [21]. Aminolevulinic acid may have a direct toxic effect as well; infected nails exposed to 100mmol of 5-ALA for 6 hours showed reduced viability of *Candida* in culture [22]. Application of the optimum concentration of ALA is important because concentrations below 100mmol do not yield sufficient amounts of PpIX to effectively inhibit growth of *T. rubrum*, but high concentrations of ALA have been found to lower the pH, causing a reduced PpIX yield [23]. Similarly, weekly applications of ALA into inoculated growth media produce less PpIX than one dose of ALA owing to the decrease in pH [23].

One concern with PDT is that treatment may not be fungicidal and only delays the progression of infection. One *in vitro* study demonstrated a nearly 50% reduction in the growth of *T. rubrum* seven days after treatment with 100mmol ALA (Schering AG, Berlin, Germany) followed by 60 minutes of exposure to an unfiltered quartz halogen [23]. However, further incubation revealed subsequent overgrowth of the fungus, possibly representing either time-delayed inhibition or overgrowth from the control side of the agar that had not been irradiated [23]. Protoporphyrin IX formation appears to occur in specific, isolated portions of the fungal conidia regardless of experimental conditions, which may explain the initial inhibition and subsequent overgrowth [23]. Another study was only able to achieve a mean kill rate of 79% of *Trichophyton interdigitorum*, short of the 90% threshold sought by the authors when utilizing 100mMol ALA and one exposure to a 635nm Paterson lamp [22]. These studies indicate that PDT may not inhibit fungal organisms completely or produce sufficient kill rates to halt a clinical infection.

Several small studies utilizing PDT for the treatment of onychomycosis have achieved exciting results. However, a larger study was not able to replicate these successes. In one case report, a patient with contraindications to oral antifungal therapy was pretreated with 40% urea under occlusion for seven days with hyperkeratosis removal and nail plate clipping, followed by application of 16 % MAL cream under occlusive dressing for three hours with subsequent exposure to 630nm broadband red light for 7.24 minutes [24]. The patient was treated with three sessions over 45 days and was found to be KOH and culture negative three months following the last treatment; this cure persisted at 24 months with no significant side effects reported [24]. Another case series used a similar protocol for two patients with onychomycosis of the fingernail caused by non-dermatophyte molds (*Fusorium oxysporum* and *Aspergillus terreus*) [25]. Each received three PDT treatments two weeks apart with 16% MAL under occlusion for four hours prior to light therapy [25]. Both patients achieved clinical cure and were culture negative at 6 month follow-up with significant improvement noted after the first session [25]. Watanabe *et al* used PDT to treat two patients with KOH-confirmed onychomycosis; both were culture negative after 6 and 7 sessions of treatment, respectively [26]. The patients underwent weekly applications of 20% urea under occlusion for 10 hours followed by application of 20% ALA methyl ester compounded in aqueous cream under occlusion for five hours with subsequent irradiation with a 630nm excimer laser [26]. These patients were treated on a weekly basis until the nails improved and were both found to be culture and KOH negative at three months post-treatment [26].

These case reports generated interest in PDT as a possible treatment for onychomycosis. However, a larger study was not able to replicate their success. In a study by Sotiriou *et al*, 30 patients with *T. rubrum*-infected toenails had a total of three treatments at two-weekly intervals [27]. Nail plates were pretreated with urea for ten days and then avulsed prior to application of 20% 5-ALA to the nail bed under occlusion for three hours; they were then irradiated with 570-670nm red light [27]. The patients were instructed not to use topical antifungal treatment unless they had more than 1 infected toenail on the foot not being treated [27]. Of the patients treated, 43.3% were clinically clear with negative microscopic exam at one year follow up, but 26.6% of these patients had residual changes affecting <10% of the nail plate; at 18 months the cure rate dropped to 36.6% [27]. In addition, all of the patients experienced pain, some to the point that therapy had to be discontinued for several minutes [27].

Discussion

Onychomycosis is a common problem with significant impact on quality of life. Current oral treatments can be ineffective, may have unacceptable side effect profiles, and are contraindicated in some patient populations. Lasers and PDT are administered locally at the site of infection, avoiding systemic side effects. Aside from pain during administration, laser and PDT are generally well tolerated. The potential efficacy of blended 870/930nm lasers, 532 or 1064nm Nd:YAG systems, and PDT have been reported by some authors. However, randomized, controlled trials in humans have not been performed.

Laser therapy may prove to be more attractive than PDT because it does not require lengthy pretreatment regimens. However, randomized studies with more patients and longer follow up are needed to assess its efficacy. The decline in clearance rate between 12 and 18 months suggests that PDT does not result in a complete cure [27]. This may be owing to the slow growth rates of *T. rubrum* or selective uptake and conversion of ALA into PpIX in isolated parts of the fungal conidia [23]. Alternatively, the optimal PDT protocol may yet be undiscovered. Alternatively, it may simply indicate these patients are more susceptible to re-infection because of dystrophic nails or for other reasons.

Part of the difficulty evaluating any therapy for onychomycosis is in distinguishing between reinfection and treatment failure. The optimal window for follow up to establish complete clinical and mycologic clearance has not been established, but the growth rate of toenails suggests testing at 18 months would be reasonable because the nail should have completely grown out by that time. In addition, factors such as repetitive nail trauma, dystrophic nails, poor nail hygiene, and diabetes predispose patients to multiple episodes of infection. Perhaps it would be more appropriate to approach onychomycosis as a chronic disease necessitating regular episodes of therapy to prevent nail dystrophy, rather than a discrete episode of infection that can be cured outright.

Because the cure rate 5 years after oral terbinafine therapy is as high as 46%, oral terbinafine is still the most effective, proven, long-term treatment for onychomycosis in patients without contraindications to oral antifungal therapy [28,29].

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