

Article

Light Therapy Effectively Treats Onychomycosis and Promotes Healthy Nail Growth in Toenails with Severe Infections: A Longitudinal Cohort Study

Alexander Rabinovich ^{1,*}, Judy Wismer ², Francesca Sarzetto ^{3,†} , Lijun Liu ⁴ and Jianping Xu ⁴ 

¹ Division of Orthopaedic Surgery, Department of Surgery, McMaster University, Hamilton, ON L8S 1C7, Canada

² Division of Dermatology, Department of Medicine, McMaster University, Hamilton, ON L8S 4K1, Canada

³ ToeFX Inc., McMaster Innovation Park, 175 Longwood Road, Suite B21, Hamilton, ON L8P 0A1, Canada; franzsarz@gmail.com

⁴ Department of Biology, McMaster University, Hamilton, ON L8S 4K1, Canada; ljliupvg@gmail.com (L.L.); jpxu@mcmaster.ca (J.X.)

* Correspondence: alex.rabinovich.md@gmail.com; Tel.: +1-289-389-8181

† Current address: Canadian Centre for Clinical Trials, 8054 Yonge St., Suite 204, Thornhill, ON L4J 1W3, Canada.

Abstract

Background: Onychomycosis is a stubborn fungal infection of the nail bed that impacts millions of people worldwide. Severe infections, such as those exhibiting deep dermatophytomas or total dystrophy, are particularly challenging to treat, and are often neglected in clinical studies of onychomycosis therapies. The purpose of this study was to evaluate the safety and efficacy of a novel light therapy suitable for severe cases of distal-lateral subungual onychomycosis. **Methods:** All infected nails received a photodisinfection regimen that entailed exposure of the whole dorsal foot surface to light, following application of a topical formula, as well as careful debridement to reduce hyperkeratosis. The protocol was administered every 2 weeks over 6 months. The length of clear healthy nail from the matrix was measured at baseline and after 6 months to evaluate new clear growth. **Results:** In total, 165 great toenails were treated in 101 patients (mean age: 61.0 ± 11.0 years, range 33–98); 153 of these nails (92.7%) had severe infections, including total dystrophy or dermatophytomas, the clinical forms most resistant to therapy. After 6 months, 120/165 nails (72.7%) showed at least a 3 mm increase in clear nail or total clearance, and 88 (53.3%) showed an increase ≥ 6 mm or clearance. The overall mean growth ($\pm$ standard deviation) was 5.9 ± 4.5 mm, with the highest growth in the group with total dystrophy (6.6 ± 4.5 mm). No side effects were reported throughout the study. **Conclusions:** Light therapy is a safe and effective treatment for severe onychomycosis, including nails with total dystrophy and dermatophytomas.

Keywords: distal-lateral subungual onychomycosis; totally dystrophic onychomycosis; dermatophytoma; light therapy; photodynamic therapy; toenails; fungal infection; photodisinfection

1. Introduction

Onychomycosis is a fungal nail infection typically caused by dermatophytes, most commonly *Trichophyton rubrum* [1]. Approximately 10–14% of the North American population is believed to be infected [1,2]. The nails affected appear yellow, brown, or discoloured,



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thickened, and crumbly; they may separate from the nail bed (onycholysis) and cause pain. The most severe cases may lead to difficulty in wearing shoes or walking and deterioration of mental health, ultimately reducing the quality of life [3].

The most common clinical form is distal-lateral subungual onychomycosis, with the fungal invasion occurring initially on the distal edge of the nail bed (hyponychium) and extending proximally, particularly along the lateral grooves [1,4]. The progressing infection can cause hyperkeratosis and onycholysis; the end-stage form of this disease involves the whole toenail and is called total dystrophic onychomycosis. The latter is characterized by complete disruption of the nail structure and possible permanent involvement of the nail matrix, severely reducing the possibility of healthy growth (Figure 1) [5].



Figure 1. Totally dystrophic onychomycosis, classified as Severe Class I cases in this study.

Totally dystrophic nails are widely accepted to be extremely difficult to treat and are rarely included in clinical studies of onychomycosis therapies, as these nails may have suffered irreversible damage to the nail matrix, permanently impairing the nail growth or appearance. Another negative prognostic factor is the presence of white, yellow, or orange longitudinal streaks or isolated patches with high concentrations of fungal hyphae (dermatophytomas), which are also particularly resistant to treatment (Figure 2) [5].

The diagnosis of this infection may be challenging, as several other nail diseases can give a similar presentation; therefore, laboratory tests confirming the presence of fungi are typically performed before starting treatment. The most commonly used tests are microscopic observation of nail samples after proper preparation, e.g., with potassium hydroxide (KOH) [4], and in vitro culture of the microorganisms, which can be used to identify the causal agent(s) [6]. Recently, polymerase chain reaction (PCR) has also gained popularity, thanks to its higher diagnostic sensitivity and specificity, as well as decreasing costs [6].

Onychomycosis is one of the most stubborn and persistent infections in humans, and there is a lack of treatment options that have been evaluated specifically for severe forms of onychomycosis. The most common treatments are systemic or topical medications; however, both options have limitations. Oral treatments should be administered daily for 12 weeks, have mycological and clinical cure rates of approximately 70% and 40%,

respectively, and may cause side effects. Topical medications are better tolerated, though they require daily applications for up to a year and have clinical cure rates lower than 20% [7]. Moreover, onychomycosis has a high frequency of relapse [2,8]. The nails are not living tissue and cannot be repaired; they can only be replaced by new growth of healthy nail, which occurs at a rate of approximately 1 mm per month in healthy nails [1,4].

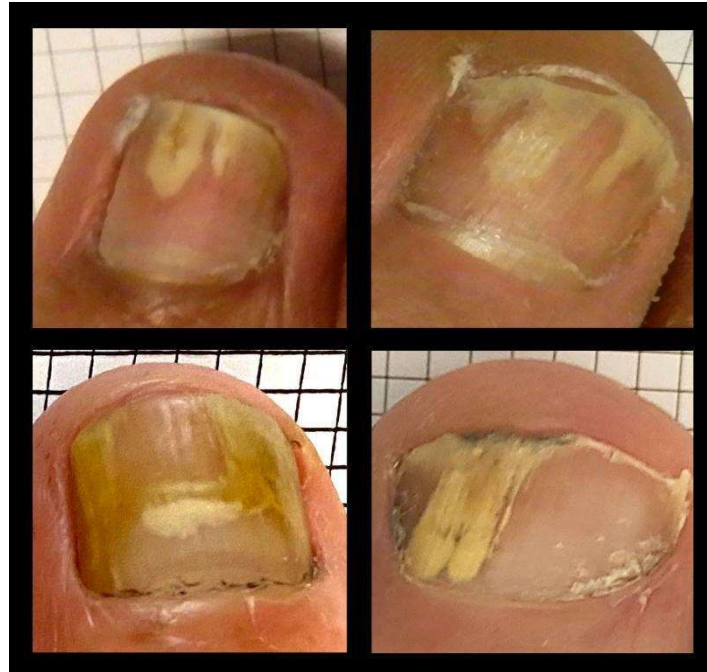


Figure 2. Onychomycosis with dermatophytomas, here classified as Severe Class II cases.

In recent years, light therapy, also called photodisinfection therapy or photodynamic therapy, has been explored as an alternative [8–10]. Light therapy has no side effects and high tolerability, which could make it an attractive option for patients with comorbidities who are unwilling or unsuitable candidates for systemic medications. This treatment entails stimulating the production of reactive oxygen species (ROS) and free radicals, which disrupt the fungal wall and eliminate the infection [11]. In contrast to most thermal laser treatments [12], which rely on heat damage to produce their therapeutic effects [13], ROS are generated from ambient oxygen via irradiation with visible light. Previous results have been promising [9,10,14]; however, to the best of our knowledge, no large clinical trials of light therapy focusing on the severest forms of onychomycosis have been conducted. Moreover, an adequate pre-treatment of the nail before light therapy application [10] and an effective photoactive agent [9] seem to be critical factors for the efficacy of the treatment.

The purpose of this study was to examine the efficacy of a new light therapy protocol on nails predominantly affected with severe onychomycosis, including totally dystrophic nails. To the best of our knowledge, this is the largest clinical study to date of a light therapy treatment protocol for severe forms of onychomycosis.

2. Methods

2.1. Patients

Patients with distal-lateral subungual or totally dystrophic onychomycosis, in one or both great toenails, were selected for this study. Clinical diagnoses were based on visual appearance (yellow or brown discoloration, hyperkeratosis, crumbly structure, onycholysis, and typical patterns, such as spikes, striae, and aurora borealis [15]); KOH microscopy, culture, and PCR tests were also performed in most cases to confirm the diagnoses. Patients

with diabetes were excluded. Patients with comorbidities such as heart disease, psoriasis, pre-diabetes, tinea pedis (athlete's foot), high cholesterol, or impaired circulation were included. Patients were required to discontinue any systemic, topical, or home antifungal remedies for at least 30 days prior to beginning the study and refrained from using other onychomycosis remedies during the study period.

The study was conducted across three centres between 2020 and 2023: Hamilton, ON, Canada (Study 1 in 2020 and Study 2 in 2021–2022), Langley, BC, Canada (Study 3, 2021), and a long-term residence for senior citizens in Windsor, ON, Canada (Study 4, 2022).

All patients provided written informed consent, and the investigational portion of the study was approved by Veritas IRB (IRB tracking number 16486-13:06:4210-02-2020, approved 12 February 2020) and allowed under an Investigational Testing Authorization by Health Canada in 2019. The study adhered to the tenets of the Declaration of Helsinki.

2.2. KOH/Culture Diagnosis

Samples of nail dust were collected and sent to a third-party laboratory (LifeLabs, Mississauga, ON, Canada) for fungal culture analysis. The analyses performed were the standard KOH test (placing a nail sample onto a microscope slide covered with potassium hydroxide, adding a stain, and reading the slide under a microscope) and fungal culture.

2.3. qPCR Diagnosis

Nail samples were collected at baseline and moved to 1.5 mL Eppendorf tubes (Eppendorf SE, Hamburg, Germany) for DNA extraction. The qPCR protocol was designed to detect dermatophytes such as the *Trichophyton* species, the most common causal agent of onychomycosis. The qPCR setting was: 10 µL of Luna mixture (New England Biolabs, Whitby, ON, Canada), 1 µL forward 10 µM primer and 1 µL reverse 10 µM primer, and 0.5 µL 10 µM probe with 7.5 µL DNA template; a total of 20 µL of this solution was added for each reaction. Three repeats were conducted for each sample, using a CFX Opus 96 Real-Time PCR System (Bio-Rad, Hercules, CA, USA) with the following protocol: (1) 95 °C for 3 min; (2) 95 °C for 10 s; (3) 64 °C for 60 s; (4) plate reading. Steps 2–4 were repeated for 41 cycles. Overall, 42 cycles were completed for this test.

2.4. Pre-Treatment Protocol

All nails were filed down on the dorsal side with a high-speed burr by a professional foot care clinician, to reduce thickness/hyperkeratosis. To mark out the areas of fungal infection and promote the production of ROS, a liquid formula (ToeFX Inc., Hamilton, ON, Canada) was applied to each nail using a disposable applicator. The formula contains a botanical extract of *Inula viscosa* (1%) with known anti-inflammatory properties [16], as well as methylthioninium chloride (0.5%), a cationic dye with a preferential affinity for the negatively charged cell walls of microorganisms like fungi.

2.5. Light Source

Red light (630–670 nm, 0.042 W/cm²) from a light-emitting diode source (ToeFX Inc.) was applied to the dorsal surface of the foot for 15 min. All toenails on the infected foot were treated regardless of whether they displayed signs of infection to limit cross-contamination between toes. The light source was not an appreciable source of heat; therefore, heat was not believed to be an operative mechanism in the destruction of the fungal cells. The light treatment acts by transferring energy to molecular oxygen in the tissues, producing ROS that lethally disrupt the fungal cell wall. These molecular products are very short-lived, and the ROS production process ceases immediately upon deactivation of the light source [11].

2.6. Frequency

Treatments were performed every 2 weeks for 6 months, for 12 treatments total. We further tested the effectiveness of occasional/infrequent light therapy treatments as a “maintenance” protocol, to retain progress after the conclusion of the regular treatment course. Patients included in this portion of the trial received additional treatment sessions every 4–6 weeks, up to 15 months after the first treatment, to establish the long-term effectiveness of the therapy. The cadence of these additional sessions was less consistent, in part due to scheduling restrictions arising from the COVID-19 pandemic.

2.7. Measurement of Clear Nail Length

All toenails were photographed at baseline and before each session to assess new nail growth. The length of new clear nail was measured at baseline, at 6 months, and at 12 months. The affected foot was placed on a sheet of standard white graph paper (3.4 × 3.4 mm grid), which served as a reference, and photographed at high resolution to discern the fine details of the infected area and measure the length of new clear nail growth. A custom software tool was used to calculate the new growth in mm.

One of the investigators (FS) selected the proximal and distal points of clear nail on each photograph, and then two vertices on the side of a single square of graph paper; the length of clear nail in mm was subsequently calculated using custom software. Figure 3 illustrates how the points of reference were selected. The length was measured as the distance from the centre of the proximal nail fold (A) to the centre of the orthogonal line of the most proximal area of dystrophy (B), in a line parallel to the longitudinal nail direction.

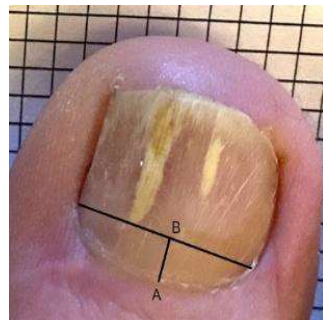


Figure 3. Measurement of clear nail. Letters A and B indicate the reference points where measurements for clear nails were taken. A: centre of the proximal nail fold; B: centre of the orthogonal line of the most proximal area of dystrophy.

At 6 months, the growth was assessed in comparison to baseline. Nails with an unclear boundary between healthy and infected portions were excluded from the analysis. The overall healthy nail lengths at baseline and after 6 months were compared with a paired *t*-test, using SPSS v. 28 (IBM, Armonk, NY, USA).

2.8. Success Criteria

As the primary outcome, a nail was considered a successful responder to the treatment when healthy growth ≥ 3 mm or complete clearance was observed, 6 months after the date of the first treatment. The overall study success criterion was to observe treatment success in $\geq 50\%$ of the treated nails. The secondary outcome was mycological cure, defined as either concurrent negative KOH and culture tests, or two consecutive negative cultures [17], 52 weeks after the date of the baseline test.

2.9. Method for Patient Surveys

Patients were administered a questionnaire at baseline, 6 and 12 months after the beginning of the treatment, including the questions “How long have you had toenail fungus?” and “Have you tried other treatments without success?” Patients also recorded personal evaluations of the changes in appearance, and their satisfaction with the treatment after its conclusion.

3. Results

A total of 206 nails from 117 patients were initially screened for inclusion in the study, with baseline assessments conducted by a professional foot care clinician. Of these, 165 nails were ultimately included in the analysis. Among them, 135 nails (from Studies 1, 2, and 4) had laboratory-confirmed onychomycosis, while the remaining 26 nails (from Study 3) were assessed solely by the clinician and an expert panel due to COVID-19-related limitations (see Table 1). However, the results of Study 3 were similar to those of the other studies, suggesting that the clinician diagnoses were accurate. The most common species identified at baseline was *Trichophyton rubrum* ($N = 107$, 79% of the 135 samples with culture; see Table 2).

Table 1. Laboratory screening test results for nails with onychomycosis.

Fungal Agent	Number of Nails Affected ($N = 135$)	Percentage of Total
<i>Trichophyton rubrum</i>	107	79%
<i>Trichophyton mentagrophytes</i>	7	5%
Other dermatophytes	13	10%
Non-dermatophyte moulds or multiple species	8	6%

Table 2. Study site information for all nails included in the analysis.

Sub-Study Number	Location	Number of Nails ($N = 165$ total)	Diagnostic Methods Used	Mean Growth (mm)
1	Hamilton, ON, Canada	23	KOH/culture	8.2 ± 5.3
2	Hamilton, ON, Canada	104	KOH/culture	4.7 ± 3.5
3	Langley, BC, Canada	26	Clinical + review panel	6.8 ± 4.8
4	Windsor, ON, Canada (long-term care facility)	12	PCR	10.0 ± 5.5

Of the 206 nails screened, 41 were excluded from the analysis, as the infected and healthy areas could not be demarcated with sufficient accuracy, either at baseline or at the endpoint. In total, 165 toenails in 101 patients (65 males and 36 females; mean age 61.0 ± 11.0 years, range 33–98 years) were included in the analysis.

The nails were divided into four groups based on the baseline presentation: (1) Severe Class III (totally dystrophic, $N = 75$, 45.4%); (2) Severe Class II (dermatophytomas present, $n = 59$, 35.7%); (3) Severe Class I (<3 mm of clear nail, but no matrix involvement, $N = 19$, 11.5%); and (4) Mild/moderate infection (≥ 3 mm of clear nail from the proximal nail fold, with no dermatophytomas; $N = 12$, 7.2%). In 125/165 nails (75.7%), the infected area reached the proximal nail fold, and no healthy nail was present at baseline.

3.1. Primary Outcome—Increase in Clear Nail in mm

Overall, 143 nails (86.7%) showed an increase in clear nail; 17 nails (10.3%) showed no change, and five (3.0%) a decrease. The mean initial healthy-nail length was 1.4 ± 3.0 mm (median and interquartile range [IQR]: 0.0 [0.0–0.0] mm, as the infection was reaching the matrix in more than 75% of nails), and it increased to 7.3 ± 4.7 mm after 6 months (median: 7.0 [3.9–12.0] mm, Figure 4); the difference between the clear length before and after the treatment was statistically significant ($p < 0.0001$). The overall mean growth ($\pm$ standard deviation) was 5.9 ± 4.5 mm (Table 3). The growth was greatest in the Severe Class III (totally dystrophic) group (6.6 ± 4.5 mm), followed by the Severe Class I (<3 mm clear nail) group (6.7 ± 4.2 mm), the Severe Class II (dermatophytomas present) group (5.0 ± 4.6 mm), and finally the mild/moderate group (4.5 ± 4.4 mm). Nails in the mild/moderate group had longer clear nail at baseline; the absolute growth was thus expected to be smaller. Figure 5 shows some representative nails that achieved treatment success.

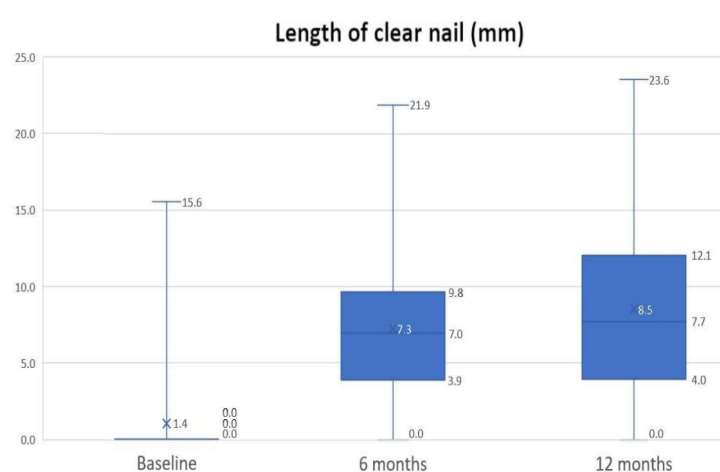


Figure 4. Length of clear nail at baseline, 6, and 12 months after first treatments. The boxes represent the interquartile range, with the median as central line and mean as a cross, and the whiskers show the full range. At baseline, more than 75% of nails had the infection reaching the matrix and thus no clear nail.

Table 3. Response to the light therapy treatment protocol after 6 months.

Outcome	Total Nails (N = 165)	Mild/Moderate Infection (≥3 mm Clear Nail) (N = 12)	All Severe Infections (N = 153)			
			Severe Class I (<3 mm Clear Nail) (N = 19)	Severe Class II (Dermatophytomas Present) (N = 59)	Severe Class III (Totally Dystrophic) (N = 75)	Total Severe (N = 153)
Any new growth	143 (86.7%)	12 (100.0%)	18 (94.7%)	48 (81.4%)	65 (86.7%)	131 (85.6%)
Growth ≥ 3 mm or total clearance, N (%)	120 (72.7%)	8 (66.7%)	15 (78.9%)	36 (61.0%)	61 (81.3%)	112 (73.2%)
Growth ≥ 6 mm or total clearance, N (%)	88 (53.3%)	7 (58.3%)	10 (52.6%)	28 (47.4%)	43 (57.3%)	81 (52.9%)
No change, N (%)	17 (10.3%)	0 (0.0%)	0 (0.0%)	7 (11.8%)	10 (13.3%)	17 (11.1%)
Decreased healthy nail, N (%)	5 (3.0%)	0 (0.0%)	1 (5.3%)	4 (6.8%)	0 (0.0%)	5 (3.3%)
Mean healthy growth (mm)	5.9 ± 4.5	4.5 ± 4.4	6.7 ± 4.2	5.0 ± 4.6	6.6 ± 4.5	6.0 ± 4.3



Figure 5. Images of representative toenails with successful outcomes, at baseline and after 6 months of treatment. Some residual blue coloration is due to the marking formula, which may be retained especially in the nail lateral skinfolds.

Overall, 120/165 nails (72.7%; 95% confidence interval [CI]: 66.3–78.1%) met the clear-nail success criterion, showing total clearance of the infection or ≥ 3 mm of new clear nail. Furthermore, 88/165 nails (53.3%; 95% CI: 46.7–60.0%) showed total clearance of the infection or ≥ 6 mm of new clear nail. The highest success rates were noted in the Severe Class III (total dystrophy) group (61/75, 81.3%) and the Severe Class I group (15/19, 78.9%).

Different results were noted in different studies, with Studies 1 and 3 having significantly higher mean growth (8.2 ± 5.3 and 6.8 ± 4.8 mm, respectively) than Study 2 (4.7 ± 3.5 mm; $p < 0.01$), whereas Study 4 only included 12 nails suitable for the analysis (among the 21 treated) and the difference was not significant.

3.2. Secondary Outcome—Mycological Cure

The secondary outcome was the mycological cure, defined as either concurrent negative KOH and culture tests or two consecutive negative cultures at 12 months or last treatment. Laboratory test results at 12 months were available for 127 of the 165 nails examined in the study (77%). We found that 75/127 nails (59.1%) achieved mycological cure as defined above (Table 4). Nails in the Severe Class III (totally dystrophic) group achieved the highest rate of mycological cure (69.1%), followed by those in the Severe Class II (dermatophytomas) group (56.5%).

Table 4. Response to occasional light therapy treatments between 6 and 12 months, for the purpose of maintaining progress made.

Outcome	Total Nails (N = 124)	Mild/Moderate Infection (≥ 3 mm Clear Nail) (N = 9)	All severe Infections (N = 115)			
			Severe Class I (< 3 mm Clear Nail) (N = 14)	Severe Class II (Dermatophytomas Present) (N = 47)	Severe Class III (Totally Dystrophic) (N = 54)	Total Severe (N = 115)
Further growth ≥ 1 mm	68 (54.8%)	4 (44.4%)	7 (50.0%)	29 (61.7%)	28 (51.9%)	64 (55.7%)
Growth ≥ 3 mm or new total clearance, N (%)	38 (30.6%)	2 (22.2%)	4 (28.6%)	17 (36.2%)	15 (27.8%)	36 (31.3%)

Table 4. Cont.

Outcome	Total Nails (N = 124)	Mild/Moderate Infection (≥3 mm Clear Nail) (N = 9)	All severe Infections (N = 115)			
			Severe Class I (<3 mm Clear Nail) (N = 14)	Severe Class II (Dermatophytomas Present) (N = 47)	Severe Class III (Totally Dystrophic) (N = 54)	Total Severe (N = 115)
Maintained clearance, N (%)	16 (12.9%)	4 (44.4%)	2 (14.3%)	4 (8.5%)	6 (11.1%)	12 (10.4%)
Stable length (±1 mm), N (%)	31 (25.0%)	4 (44.4%)	4 (28.6%)	10 (21.3%)	13 (24.1%)	27 (23.5%)
Decreased healthy nail > 1 mm, N (%)	25 (20.1%)	1 (11.1%)	3 (21.4%)	8 (17.0%)	13 (24.1%)	24 (20.9%)
Mean healthy growth (mm)	1.6 ± 3.6	1.6 ± 3.6	1.4 ± 4.5	2.0 ± 3.9	1.4 ± 3.1	1.6 ± 3.6
Mycological cure * (N = 127 lab results available)	75/127 (59.1%)	5/10 (50.0%)	6/16 (37.5%)	26/46 (56.5%)	38/55 (69.1%)	70/117 (59.8%)

* Mycological cure was defined as either concurrent negative KOH and culture tests or two consecutive negative cultures at 12 months or last treatment.

3.3. Patient Surveys

No adverse effects or reports of pain or discomfort were recorded during the trials. In total, 82 patients completed a survey at the end of the treatment, though not every patient answered every question (Table 5); among these, 76 (92.7%) reported that their toenails appeared better or much better than before, whereas four (4.9%) said they were about the same, and two (2.4%) noticed a worsening. In response to the question “How long have you had toenail fungus?”, 56/76 patients (73.7%) reported 5 years or more, and 74/82 (90.2%) also reported having tried at least one other approach without success prior to their participation in the study.

Table 5. Patient survey results.

Questions and Response Categories	Responses, N (%)
How long have you had toenail fungus?	N = 76 total
<5 years	20 (26.3%)
5–10 years	20 (26.3%)
10–20 years	20 (26.3%)
>20 years	16 (21.0%)
Have you tried one or more other treatments before without success?	N = 82 total
No	8 (9.8%)
Yes	74 (90.2%)
Oral medications	14 (18.9%)
Prescription topical medications	28 (37.8%)
Laser	7 (9.4%)
Non-prescription medications	26 (35.1%)
Home remedies	43 (58.1%)
How do your toenails look at the end of the treatment?	N = 82 total
Much better than before/Better than before	76 (92.7%)
About the same	4 (4.9%)
Worse than before	2 (2.4%)

4. Discussion

This study examined a novel light therapy treatment for nails predominantly afflicted with severe and highly severe onychomycosis, including totally dystrophic nails and nails with dermatophytomas. These presentations are considered challenging to treat, as the involvement of the matrix and pockets of high fungal load hinder the efficacy of treatments and reduce the capacity for healthy growth. Nails showing clear growth ≥ 3 mm or complete clearance were considered to have a successful outcome, and the overall treatment success goal was $\geq 50\%$ of the nails achieving individual success.

In total, 72.7% met the primary outcome of treatment success (>3 mm of growth or total clearance). Interestingly, nails that were severely infected or totally dystrophic showed the greatest absolute improvements. This result might be attributed to more extensive debridement that was performed to severely affected nails, allowing for greater light penetration into the nail bed, where the fungal organism typically resides.

Different study sites yielded significantly different outcomes, despite controlling for patient-related factors, such as infection severity and age, between studies. A retrospective evaluation of a sample of pictures showed that the debridement performed by the foot care clinicians in Studies 1 and 3 was more thorough than in Study 2; therefore, variability between study sites is believed to be due to differences in the debridement technique. Pre-treatment nail preparations such as debridement or application of urea have been previously suggested in the literature [10] as a critical factor for the light treatment success; it is purported that thinner nails allow deeper penetration of the light into the nail bed (which is typically the locus of the infection).

Similar results have been reported before in small clinical trials using light therapy, conducted mostly on nails with mild/moderate infection [18–22]. However, to the best of our knowledge, larger clinical studies have not been conducted, and previous studies did not specify the number of patients with severe onychomycosis, or excluded them completely [9,23,24]. We believe that the present study is the first large clinical trial of light therapy performed primarily on toenails with severe onychomycosis.

Comparison to Other Antifungal Therapies

It can be difficult to compare different therapies for onychomycosis due to different definitions of success, and differences in infection severity at baseline. We therefore have presented comparisons in three different categories: light therapy devices, oral antifungals, and topical antifungals, using the most commonly employed metrics in each.

- (a) Comparison to other light therapy devices.

The results herein are similar to those reported in a previous study of the Lunula LaserTM (Erchonia Corporation, McKinney, TX, USA), a non-thermal laser device [13], which was administered to patients once a week for four weeks. The study reported that 36/54 nails (67%) achieved growth ≥ 3 mm, 6 months after the start of treatment, with a mean growth of 5.18 mm. These results are comparable to those of the present study, with 73% of patients achieving the succession criterion and a mean growth of 5.7 mm. It is noteworthy that the Lunula LaserTM study considered nails only with ≥ 2 mm of clear nail at baseline and excluded nails with totally dystrophic onychomycosis and dermatophytomas. The present study included such cases, demonstrating that light therapy can be effective even for nails with highly severe infections.

- (b) Comparison to oral antifungals.

Oral medications (e.g., itraconazole, fluconazole, and terbinafine) have the highest mycological cure rates (up to 70% at 48 weeks, with terbinafine, compared to the 58% at 52 weeks that we report herein) and are used for the most severe cases [3,8,25]. However, prolonged courses are required (at least 12 weeks of daily administration),

compliance may be low, and the risk of side effects and drug interactions can make this option unsuitable for patients with comorbidities, particularly liver diseases [8]. We also note that unlike with light therapy, the efficacy of antifungal pharmaceuticals depends on the causative agent [8,26]; this is expected to be a further limitation for oral therapies, as antifungal resistance is reportedly increasing worldwide [26]. Terbinafine targets dermatophytes like *T. rubrum* and *T. mentagrophytes*; it is thus not effective against those in the genus *Candida*, or against non-dermatophyte moulds. Finally, it is worth noting that a study directly comparing regimens of light therapy versus fluconazole reported that the light therapy was more effective in providing clinical cure [20].

- (c) Comparison to topical antifungals.
Topical creams (e.g., efinaconazole, ciclopirox, tavaborole) are also widely prescribed [3,25]. They are more easily tolerated than the oral medications and have a lower risk of side effects; however, they require daily applications for up to 48 weeks, with consequent lower compliance, and have lower efficacy than oral medications. A study of patients with mild-to-moderate onychomycosis only (no dermatophytomas or matrix involvement) treated with the topical drug efinaconazole reported a mycological cure rate of 53.4–55.2% [27]. By contrast, we report herein an overall mycological cure of 59.1%, but with 92.7% of initial infections assessed as severe to extremely severe (with dermatophytomas and matrix involvement included).

Overall, the light therapy protocol described herein is slightly less effective than the best oral treatment for severe infections and is more effective than the most common topical treatment for moderate infections. However, it does not require a daily commitment and is thus more conducive to patient compliance; moreover, it has no side effects and can be administered safely to patients with comorbidities.

This study demonstrated that light therapy is an effective non-pharmaceutical treatment for onychomycosis, promoting healthy nail growth even in severely infected nails. Furthermore, a specific advantage of the light therapy examined in this study is that it targets all genii of fungi, rendering it an effective agent against various and mixed-species infections, and is unlikely to develop fungal resistance, in contrast to a growing global trend with antifungal agents [9].

The success of this treatment, like that of all antifungal therapies, will be improved by strategies to reduce the risk of re-infection, including frequent sanitation of shoes, socks, and textiles, proper hygiene and drying of feet and nails, and avoiding walking bare foot in humid and public places, as relapse and cross-contamination are common [2,26].

This study has some limitations: the diagnostic criteria and treatment protocols changed slightly across different study sites, and debridement was inconsistent, as different clinicians might have employed different burrs, drills, drill speeds, and techniques. These limitations will be addressed in a further Phase III clinical study.

5. Conclusions

A light-therapy treatment administered over 6 months, combined with thorough debriding, is safe and effective for most patients with onychomycosis, even those with the most severe forms of infection. Healthy growth was observed in 87% of nails, and 73% achieved the desired treatment outcome of at least 3 mm of new nail growth, with mycological cure recorded for 59% of nails. The therapy required no daily commitment and had no recorded side effects, in contrast to oral therapies. Therefore, this protocol represents a viable treatment option for patients, particularly those with severe infections, impaired mobility, comorbidities, or the desire to avoid pharmaceutical remedies.

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Data Availability Statement: The raw data supporting the conclusions of this article will be made available by the authors on request.

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