The Egyptian Journal of Hospital Medicine (July 2018) Vol. 72 (4), Page 4313-4319

Evaluation of the clinical efficacy of Fractional CO^2 laser combined with topical antifungal in the treatment of onychomycosis using SCIO (Score clinical index of onychomycosis)

Norhan K.M. Ali Al-Meligi; Maha A. Shaheen; Mohammed T. Mahmoud; Rania M. Al Husseiny

Dermatology, Venerology and Andrology Department, Faculty of Medicine - Ain Shams University

Corresponding: Norhan K.M. Ali Al-Meligi, norhankhaledderma@gmail.com, **Tel:** +202 01099978172

ABSTRACT

Background: Onychomycosis, a fungal infection of the nail, is considered one of the most prevalent disorders of the nail. Score clinical index of onychomycosis (SCIO) enable comparison of the severity of onychomycosis between nails despite differences in the clinical presentation. Recently fractional CO2 laser and topical antifungal were found to be effective in treating onychomycosis.

Aim of the Work: To evaluate the clinical efficacy of fractional carbon dioxide laser combined with topical antifungal in treatment of onychomycosis.

Patients and Methods: The present study included 20 patients with toenail and fingernail onychomycosis of all age groups. The affected nails received 3 sessions of laser therapy (Fractional CO2 laser) at 4 weeks intervals and once daily application of topical antifungal (Oxiconazole) available at the market under the name tinox cream.

Conclusion: We concluded that fractional carbon-dioxide laser therapy, combined with a topical antifungal agent, is effective in the treatment of onychomycosis. It can treat different types of onychomycosis safely and effectively, and is especially suitable for older patients with low immunity or liver and renal dysfunction who are not appropriate candidates for systemic antifungal agents. Thus, it could be considered as an alternative treatment modality.

Keywords: CO2: Carbon dioxide; DLSO: Distal-lateral subungual onychomycosis; SCIO: Score clinical index of onychomycosis

INTRODUCTION

Onychomycosis, a fungal infection of the nail, is considered one of the most prevalent disorders of the nail. It occurs after primary infection of the nail bed, which may lead to subungual hyperkeratosis [(1)]. Primary caused by dermatophytes such as Trichophyton rubrum and Trichophyton mentagrophytes [(2)]. Other causative organisms are non-dermatophyte molds [(3)]. Candida albicans accounts for approximately 70% of onychomycosis caused by yeasts. Direct microscopic examination after (KOH) preparation and fungal culture are commonly used to confirm the diagnosis [(4)].

The classical treatment modalities for onychomycosis include oral as well as topical antifungal, however, the cure rate is considered to be low and regression rate is found to be high [(5)].Topical antifungals are often ineffective because of their inability to penetrate via nail plate. Systemic treatments, although effective, have limited application because of adverse effects such as hepatotoxicity, potential drug interactions [(6)].

Score clinical index of onychomycosis (SCIO) enable comparison of the severity of onychomycosis between nails despite differences in the clinical presentation, The SCIO may prove to be an accurate indicator of therapeutic effectiveness [(7)]. It has:

Clinical pattern component based on (1) clinical form, (2) depth of nail involvement and, (3) thickness of subungual hyperkeratosis.

Growth pattern component based on location of the onychomycosis, digit number and age of the patient.

Photodynamic therapy is considered to be a new non-traditional method for treatment of onychomycosis [(8)]. Photodynamic therapy offers a number of advantages over traditional antimicrobial therapies as it has a broad spectrum action and is effective independent of patterns of antimicrobial resistance [(9)]. Laser-based treatments have been explored as a possible alternative treatment for onychomycosis. Long pulse 1064-nm neodymium: yttrium-aluminiumgarnet (Nd:YAG) laser, diode laser and Q-switched Nd:YAG laser have all been studied and found to be safe and effective for treating onychomycosis.

The fractional CO2 laser systems were developed to maximize the effect of ablative laser therapies and minimize side effects [(10)]. Recently fractional CO2 laser and topical antifungal were found to be effective in treating toenail onychomycosis [(4)].

AIM OF THE WORK

To evaluate the clinical efficacy of fractional carbon dioxide laser combined with topical antifungal in treatment of onychomycosis.

Received:7/4/2018
Accepted:16/4/2018

PATIENTS AND METHODS

Patients

The present study included 20 patients with toenail and fingernail onychomycosis of all age groups. The study was approved by the Research Ethical Committee, Faculty of Medicine, Ain Shams University and fulfilled all the ethical aspects required in human research. All patients received full information about description of the procedure of treatment, possible side effects, photo documentation and they all provided written consent.

Inclusion criteria: Patients of both sex. All age groups. Onychomycosis of toe and finger of all types (Distal and lateral subungual onychomycosis, Proximal subungual onychomycosis, Superficial white onychomycosis, Total dystrophic onychomycosis).

Exclusion criteria: Patients complaining of other diseases causing nail dystrophy e.g. psoriasis and lichen. Patients with immunosuppression and diabetes. Patients with previous history of previous systemic antifungal treatment of onychomycosis within the last 3 months or topical treatment within the last month.

All patients were subjected to the following: Full history taking including onset, course and duration of onychomycosis, family history, previous treatment methods used and history of other diseases. General examination to exclude systemic diseases. Dermatological examination. Local examination of the nail and calculation of score clinical index of onychomycosis (SCIO). Mycological examination (KOH 20 % and 4 fungal culture) at the beginning of the study to confirm the diagnosis and at the end of laser sessions to evaluate treatment as regards mycological cure. The affected nails received 3 sessions of laser therapy (Fractional CO2 laser) at 4 weeks intervals and once daily application of topical antifungal (Oxiconazole) available at the market under the name tinox cream. Evaluation of treatment response was done through photography using (iphone 6 camera 8 megapixel 1/3 inch sensor with 1.5 micro m pixel size) (at the beginning of the study, at the end of laser session and after 3 months of treatment), calculation of Score clinical index of onychomycosis (at the beginning of the study, at the end of laser sessions and after 3 months of treatment) using available online electronic calculator available at (www.onychoindex.com.)[11]. Furthermore, patient's satisfaction 3 months after treatment was rated using a visual analog scale (VAS; A rating of 0 for no satisfaction, and a rating of 10 for the best possible satisfaction), as well as KOH and fungal culture at the beginning of study and at the end of laser sessions to evaluate mycological cure.

Assessment of treatment complications:

Pain: Patients were examined immediately after each session to evaluate post procedural pain and asked to rate the pain intensity as a number from zero to ten using numerical rating scale (NRS). It is a 0 to 10 point scale which correlates to no pain at zero, mild pain from 1-4, moderate pain from 5-7 and severe pain from 8-10.

Others: Patients were also evaluated for other post fractional CO2 laser complications e.g. nail hematoma, dystrophy and onycholysis.

Methods:

Steps of Mycological Examination:

Collection of nail scrapings: Nail scrapings: obtained by waxy carver and collected in sterile disposable 9 mm petri dishes, it was used for KOH microscopic examination and culture.

Direct Microscopic Examination:

Nail scrapings: Particles of nail scrapings were added to two drops of 20 % KOH and covered with a cover slide, gently heated over an open flame then examined after half an hour under the light microscope for demonstration of fungal elements e.g. yeast cells, hyphae, pseudohyphae, spores and branched septate hyphae.

Culture: Particles of nail scrapings from each specimen were inoculated in 3-4 sites of two tubes of SDA+ chloramphenicol and two tubes of dermatophyte test medium agar then incubated at 30 degree C and observed for growth every other day, during an incubation periods of 3 weeks.

Score Clinical Index of Onychomycosis (SCIO): The SCIO enables comparison of the severity of onychomycosis between nails despite differences in the clinical presentation and demographics. The SCIO index proved to be an accurate indicator of therapeutic effectiveness (7). Clinical pattern component:

The clinical pattern component of the SCIO is divided into (1) clinical form, (2) depth of

nail involvement and, (3) thickness of subungual hyperkeratosis (Table 1) [7].

Table (1): The clinical pattern component of the SCIO [7].

Key Factor	Grade 1	Grade 2	Grade 3
Clinical form (f)	DLSO	SWO	PSO
Depth of involvement (d)	<1/3	1/3 to 2/3	>2/3
Degree of hyperkeratosis (h)	absent or< 1mm	1 – 2 mm	> 2 mm

Growth component:

The SCIO has a growth component in addition to the clinical index component, and this is based on the location of the onychomycosis (fingernail or toenail, digit number) and the age of the patient. (Table 2) (7).

Table (2): Growth component of the SCIO [7].

Key Factor	Grade 1	Grade 2	Grade 3
Location	II – V fingernails	Thumbnail or II – V toenails	Big toenail
Age of patient, years (a)	<25	25-60	>60

The growth component reflects the amount of therapy required for onychomycosis. A higher SCIO index suggests that the onychomycosis may be more severe and thereby require more prolonged treatment [7].

Laser Machine:

The fractional CO2 laser used in this study was BISON Fire-Xel Fractional CO2 laser, (made in Korea) (Figure 1).

Figure (1): BISON Fire-Xel Fractional CO2 laser.

The parameters used were (scanner mode: pulse width 4,000 ms, repeat delay single, overlap 3 times, density 0.5 mm, energy 180 mj/cm2 and spot size of 3 mm x 3 mm).

Data Management and Analysis: The collected data was revised, coded, tabulated and introduced to a PC using statistical package for social science (IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp). Data was presented and suitable analysis was done according to the type of data obtained for each parameter.

Descriptive statistics: Mean, standard deviation (± SD) and range for parametric numerical data, while median and interquartile range (IQR) for non-parametric numerical data. Frequency and percentage of non-numerical data.

Analytical statistics: Student T Test was used to assess the statistical significance of the difference between two study group means. Mann Whitney Test (U test) was used to assess the statistical significance of the difference of a non-parametric variable between two study groups. Correlation analysis (using Pearson's or spearmen method): To assess the strength of association between two quantitative variables. The correlation coefficient denoted symbolically "r" defines the strength and direction of the linear relationship between two variables. The Friedman test was used to assess statistical significance of the difference of a non-parametric variable measured more than two times for the same study group. P- value: level of significance: -P>0.05: Non significant (NS). -P< 0.05: Significant (S). -P<0.01: Highly significant (HS).

RESULTS

I- Clinical evaluation:

Demographic data: The present study included 20 patients with toe nail or finger nail onychomycosis attending the Dermatology Outpatient Clinic of Ain Shams University Hospitals from July 2017 to January 2018. The age of patients ranged from 12 to 55 years old with a mean age of 33 years ± 12.4 SD. The females represented the majority of cases (95%) (Table 3).

Table (3): Description of demographic data among study cases.

		Mean	±SD	Minimum	Maximum
Age		33.0	12.4	12.0	55.0
		N	%		
Gender	Male	1	5.0%		
	Female	19	95.0%		

Clinical disease characteristics among study cases: The disease duration among study cases ranged from 2 months to 5 years with a mean of 1.8 ± 1.4 years SD. The main site of fungal infection was finger nail (15 cases), (75 %). The main clinical type of onychomycosis was distal and lateral subungual onychomycosis (19 cases) (95.0

%). The causative organisms of onychomycosis was Aspergillus species (14 cases) (70.0 %) and (6 cases) of candida species (30 %) (Table 4).

Table (4): Description of clinical disease characteristics among study cases.

		Mean	±SD	Minimum	Maximum
Disease duration		1.8	1.4	0.2	5.0
		N	%		
Site of infection	Finger nail	15	75.0%		
	Toe nail	5	25.0%		
Clinical Type	DLSO	19	95.0%		
	SWO	1	5.0%		
Type of organism	Aspergillus	14	70.0%		
	Candida	6	30.0%		

Evaluation of treatment response: Assessment of treatment response according to patient's satisfaction: Patients were asked to rate their treatment satisfaction 3 months after treatment using VAS. The mean of patient's satisfaction score was 8.1 ± 2.0 SD. (Table 5).

Table (5): Patient's satisfaction after treatment .

	Mean	±SD	Minimum	Maximum
Patient satisfaction	8.1	2.0	2.0	10.0

Assessment of treatment response according to score clinical index of onychomycosis (SCIO): SCIO was calculated at the beginning of the study, at the end of laser sessions and after 3 months of treatment. There was a highly significant difference between the 3 SCIO measurements (P value =0.001) (Table 6 and figure 2). 85 % of cases showed clinical improvement, only one case showed clinical relapse according to SCIO (after clinical improvement and mycological cure) 3 months after treatment months, while mycological relapse could not be detected as fungal cultures were not repeated 3 months after treatment.

Table (6): Comparison between SCIO at baseline, at the end of laser sessions (at 3 months) and after 3 months of treatment among study cases (at 6 months).

	Mean	±SD	Median	IQR		P	Sig
SCIO baseline	8.95	4.66	8.0	5.0	12.7	0.001*	HS
SCIO 3 months	6.22	4.07	6.1	3.7	8.4		
SCIO 6 months	4.97	4.97	8.0	5.0	12.7		

* Freidman test

3. Assessment of treatment response according to KOH and mycologiacal culture

KOH and fungal culture were done at the beginning of the study and repeated at the end of laser sessions for evaluation of mycological cure regardless the clinical improvement. 14 cases (70.0 %) showed organism clearance (negative KOH and culture at the end of laser sessions). While 6 cases (30 were KOH and culture positive for Aspergillus niger, Aspergillus glaucus, Aspergillus versicolor, candida and cladosporium) after 3 months of treatment (Table 7, Figure 3).

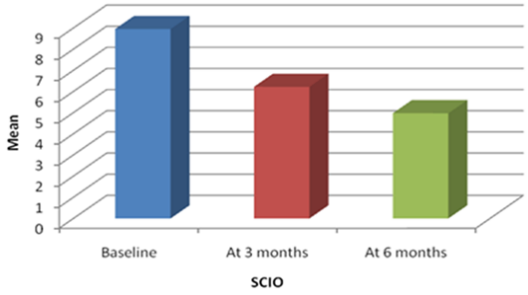

Figure (2): Comparison between SCIO at baseline, at the end of laser sessions and after 3 months of treatment among study cases.

Table (7): Assessment of treatment response according to KOH and mycologiacal culture.

	Mean	±SD	
Organism clearance after treatment	Yes	14	70.0%
	No	6	30.0%

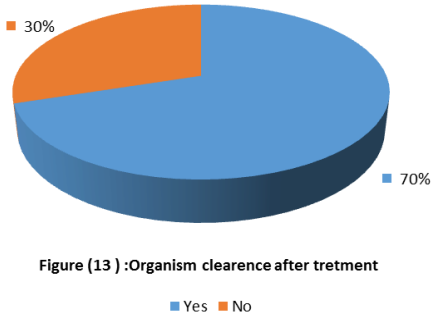

Figure (3): Organism clearance after treatment.

Correlation between demographic data, clinical disease characteristics and treatment response:

There was no significant correlation between age of the patient or disease duration and patient satisfaction [(P= 0.274) and (P= 0.647)] respectively (Table 8).

Table (8): Correlations between each of age, disease duration and patient satisfaction.

		Patient satisfaction
Age	r	-.257
	p	.274
	sig	NS
Disease duration	r	.109
	p	.647
	sig	NS

There was no significant correlation between age of the patient and SCIO at baseline (P= 0.095), at

the end of laser sessions (P= 0.090) and after 3 months of treatment (P= 0.152) after treatment (Table 9).

Table (9): Correlations between of age of patients and SCIO at baseline, at the end of laser sessions and after 3 months of treatment.

		SCIO at baseline	SCIO (at end of laser sessions)	SCIO (after 3 months of treatment)
Age	r	0.384	0.389	0.333
	P	0.095	0.090	0.152
	Sig	NS	NS	NS

Beside, no significant correlation was found between duration of the disease and SCIO at baseline (P= 0.854), at the end of laser sessions (P= 0.644) and after 3 months of treatment (P= 0.297) after treatment (Table 10).

Table (10): Correlations between disease duration and SCIO at baseline, 3 months and after 3 months of treatment.

		SCIO 1st	SCIO 3rd	SCIO 6th
Disease duration	r	-0.044	-0.110	-0.245
	P	0.854	0.644	0.297
	Sig	NS	NS	NS

Furthermore, on correlation between age of patient or disease duration and change or percent of change in SCIO seen after 3 months of treatment from baseline; no significant correlation was found (P= 0.868) (P =0.236) and (P= 0.201) (P=0.319) respectively (Table 11).

Table (11): Correlations between age of patient or disease duration and the change or percent of change in SCIO at 6 months from baseline.

		SCIO change	SCIO % of change
Age	R	0.040	-0.278
	P	0.868	0.236
	Sig	NS	NS
Disease duration	R	0.299	0.235
	P	0.201	0.319
	Sig	NS	NS

There was no significant correlation between site of infection and each of change and percent of change in SCIO at 6 months from baseline Table (12).

Table (12): Comparison between Site of infection and each of change and percent of change in SCIO (at 6 months) from baseline.

	Site of infection										P	Sig
	Finger					Toe						
	Mean	±SD	Median	IQR		Mean	±SD	Median	IQR			
SCIO change	3.72	3.46	3.4	1.6	5.4	4.72	3.48	4	3.3	8.0	>0.05	NS
SCIO % of change	57.8	36.08	67.5	34	75.76	39.79	28.8	50	19.8	62.4	>0.05	NS

**Mann Whitney test

Also, there was no significant correlation between Site of infection and patient's satisfaction (P =0.661).Table (13).

Table (13): Comparison between Site of infection and patient's satisfaction.

		Patient satisfaction		P*	Sig
		Mean	SD		
Site of infection	Finger	7.93	2.15	>0.05	NS
	Toe	8.40	1.52		

*student t test

There was no significant correlation between type of organism and each of change and percent of change in SCIO at 6 months from baseline. Table (14)

Table (14): Correlations between type of organism and each of change and percent of change in SCIO (at 6 months) from baseline.

	Type of organism										P*	Sig
	Aspergillus					Candida						
	Mean	±SD	Median	IQR		Mean	±SD	Median	IQR			
SCIO change	3.41	3.16	3.3	1.6	5.4	5.27	3.89	4.2	3.3	6.7	>0.05	NS
SCIO % of change	45.54	34.67	56.2	24.24	67.50	71.4	29.41	70.75	67	100	>0.05	NS

*Mann Whitney test

Also, no significant correlation between type of organism and patient's satisfaction (p 0.378).Table (15)

Table (15): Comparison between type of organism and patient's satisfaction.

		Patient satisfaction		P**	Sig
		Mean	±SD		
Type of organism	Aspergillus	7.79	2.29	0.378	NS
	Candida	8.67	.82		
	Yes	7.71	2.09		

**student t test

There was a significant positive correlation between change and percent of change in SCIO at 6 months from baseline and patient satisfaction score (Table 16).

Table (16): Correlations between patient satisfaction and each of change and percent of change in SCIO from baseline.

		SCIO change	SCIO % of change
Patient satisfaction	R	0.503*	0.719**
	P	0.024	0.0001
	Sig	S	HS

DISCUSSION

Our results confirmed the efficacy of fractional CO2 laser combined with topical antifungal in treatment of onychomycosis. The mean of patient's satisfaction score was 8.1 ± 2.0 SD. There was a highly significant difference

between SCIO at baseline and at the end of laser sessions with lower levels at the end of laser sessions (P value =0.001) (90 % of cases showed clinical improvement with only 70 % of cases showed mycological cure (negative culture and KOH) seen at that time. Similarly, there was a highly significant difference between SCIO at baseline and after 3 months of treatment with lower levels after 3 months of treatment (P value =0.001) (85 % of cases showed clinical improvement), only one case showed clinical relapse according to SCIO (after clinical improvement and mycological cure) 3 months after treatment months, while mycological relapse could not be detected as fungal cultures were not repeated 3 months after treatment.

These findings are in agreement with ***Lim et al.*** [11], ***Bhatta et al.*** [4] and ***Zhou et al.*** [12].

A study done by ***Lim et al.*** [11] where 24 patients treated with 3 sessions of fractional carbon-dioxide laser therapy at 4 weeks interval and a topical antifungal cream (amorolfine cream). Significant clinical improvement was observed visually as the appearance of most of the treated nails improved substantially compared to baseline. The overall treatment efficacy was determined by comparing the infected area at baseline and 3 months using 4 grades scale as follows: complete response (fully normal-appearing nail measured from the proximal nail fold to involved nail), moderate response (20%-60% normal-appearing nail), and no response (20% normal-appearing nail). Furthermore, direct microscopic examination using potassium hydroxide and fungal culture were performed in case of complete clearance. A total of 22 patients (92%) showed a clinical response, whereas 12 patients (50%) showed a complete response with a negative microscopic result. Only 2 patients (8%) showed no improvement after final treatment. In all of the patients showing a complete response, there was no clinical or mycological recurrence at 3 months after the last treatment.

Another study reported by ***Bhatta et al.*** [4] where 75 patients received 3 sessions of laser therapy at 4-week intervals and once-daily application of terbinafine cream for 3 months. They reported that 94.66 and 92% of the treated patients showed negativity for KOH examination and fungal culture respectively 3 months after treatment. However only 80% were culture negative at 6 months of follow-up.

Zhou et al. [12] studied 2 groups of patients with onychomycosis. The first group only received 12 sessions of fractional CO2 laser treatment at 2-week interval for 6 months. The second group received 12 sessions of laser treatment combined with luliconazole 1% cream once daily for 6 months. The second group showed both significantly higher clinical efficacy rate (69.6% vs 50.9%) and mycological clearance rate (57.4% vs 38.9%) compared with 1st group 3 months after the treatment.

Most of the previous studies used clinical efficacy rate as a method of clinical evaluation while ***Bhatta et al.*** [4] and our study used instead SCIO. The SCIO enabled comparison of the severity of onychomycosis between nails despite differences in the clinical presentation and demographics.

Regarding treatment complications of our study; the mean of pain score was 5.9± 2.9 SD (moderate pain), the age of the patient and disease duration did not affect pain score. These findings are in agreement with ***Lim et al.*** [11] and ***Zhou et al.*** [12]. Furthermore, similarly to ***Lim et al.*** [11] no immediate bleeding or oozing was observed.

CONCLUSION

We concluded that fractional carbon-dioxide laser therapy, combined with a topical antifungal agent, is effective in the treatment of onychomycosis. It can treat different types of onychomycosis safely and effectively, and is especially suitable for older patients with low immunity or liver and renal dysfunction who are not appropriate candidates for systemic antifungal agents. Thus, it could be considered as an alternative treatment modality.

REFERENCES

1. **Bhatta AK, Huang X, Keyal U *et al.* (2015):** Laser treatment foronychomycosis: a review. Mycoses, 57: 734-740.
2. **Gupta A and Nakrieko K (2014):** Molecular determination of mixed infections of dermatophytes and nondermatophyte moulds in individuals with onychomycosis. J Am Podiatr Med Assoc., 104 (4): 330-336.
3. **Sreepurna A T, Jishnu B T, Thanneru V *et al.* (2017):** An assessment of in vitro antifungal activities of efinaconazole and itraconazole against commom non dematophyte fungi causing onychomycosis. Journal of fungi, 3 (2): 20.

4. **Bhatta A, Keyal U, Huang X *et al.* (2015):** Fractional carbon-dioxide (CO laser-assisted topical therapy for the treatment of onychomycosis. J Am Acad Dermatol., 74(5):916-23.
5. **Gupta AK, Cooper EA and Paquet M (2013):** Recurrences of dermatophyte toenail onychomycosis during long-term followup after successful treatments with mono- and combinedtherapy of terbinafine and itraconazole. J Cutan Med Surg., 17 (3): 201-206.
6. **Scher RK, Rich P, Pariser D *et al.* (2013):** The epidemiology, etiology, Pathophysiology of onychomycosis.Semin cutan Med Surg., 32: s2-s4.
7. **Gupta A, Sergeev A, Sergeev Y *et al.* (2002):** The scoring clinical index for onychomycosis. Skin therapy letter,7: 6-7.
8. **Grover C and Khurana A (2012):** An update on treatment of onychomycosis. Mycoses, 55: 541-551.
9. **Robres P, Aspiroz c,, Rezusta A *et al.* (2015):** Usefulness of photodynamic therapy in the management of onychomycosis. Actas Dermosifiliogr, 106 (10): 795-805.
10. **Tierney EP, Eisen RF and Hanke CW (2011):** Fractionated CO laser skin rejuvenation. Dermatol Ther., 24: 41-53.
11. **Lim EH, Kim HR, Park YO *et al.* (2014):** Toe nail onychomycosis treated with a fractional carbon-dioxide laser and topical antifungal cream. J Am Acad Dermatol., 70 (5): 918-23.
12. **Zhou B, MD, Yan LU, Permatasari FT *et al.* (2016):** The efficacy of fractional carbon dioxide (CO2 laser combined with luliconazole 1% cream for the treatment of onychomycosis. Medicine (Baltimore), 95(44):e5141.