Dermatologia Kliniczna 2013, 15 (2): 67-70
ISSN 1730-7201

Onychomycosis with dermatophytoma. A comparison among the results of treatments with oral terbinafine, topical 40% urea in monotherapy and combination therapy

Grzybica paznokci z towarzyszącą grzybicą skóry (*dermatophytoma*). Porównanie wyników leczenia: doustną terbinafiną, miejscowo stosowanym 40% kremem z mocznikiem w monoterapii z terapią łączoną

Karen Escalante[1], Erick Martínez[2], Edoardo Torres-Guerrero[3], Stefanie Arroyo[3], Roberto Arenas[3]

[1] Dermoclinic, San Salvador City, El Salvador

[2] Medical Mycology Unit, Institute of Dermatology and Skin surgery "Prof. Dr. Fernando A. Cordero C.", Guatemala City

[3] Mycology Section, "Dr. Manuel Gea González" General Hospital, Mexico City, Mexico

ABSTRACT

Background: Onychomycosis is the most frequent and recalcitrant onychopathy, with cure rates ranging from 35% to 50% with oral terbinafine. Dermatophytoma is a mass of fungal hyphae and spores which can be observed under direct microscopy and is frequently resistant to treatment.
Objective: To evaluate effectiveness of monotherapy with oral terbinafine, topical 40% urea and combination therapy of both drugs in patients with onychomycosis and dermatophytoma.
Material and methods: We studied 55 patients, attending the outpatient dermatology clinic, during six months period. An open, prospective, longitudinal and comparative study was performed. All cases with onychomycosis and dermatophytoma of toenails were confirmed by potassium hydroxide (KOH) and culture. 40 patients completed the study and the follow-up. Results were analyzed according to clinical and mycological improvement 12 weeks after completing 3 months of treatment. Chi-square test was used.
Results: Clinical cure was achieved in 50% of the group with the combination therapy group, 42% with oral terbinafine and 7% with occlusive 40% urea cream at the 24th week. Mycological cure with combined therapy reached 93%, with terbinafine – 67% and with 40% urea cream – 14%.
Conclusions: Treatment with the combination therapy of oral terbinafine and 40% urea cream in onychomycosis with dermatophytoma is more effective than both monotherapies.

Key words: onychomycosis, dermatophytoma, Trichophyton rubrum, Trichophyton mentagrophytes, terbinafine, urea

STRESZCZENIE

Wprowadzenie: Grzybica paznokci stanowi najczęściej występującą i oporną na leczenie patologię płytki paznokciowej. Skuteczność monoterapii doustną terbinafiną wynosi od 35 do 50% leczonych. *Dermatophytoma* jest odmianą grzybicy paznokci, w której dochodzi do masywnej inwazji grzybiczej płytki paznokciowej, co można stwierdzić w bezpośrednim badaniu mikologicznym. Najczęściej przypadki te są oporne na leczenie.
Cel pracy: Porównanie skuteczności leczenia grzybica paznokci z towarzyszącą grzybicą skóry (*dermatophytoma*) doustną terbinafiną, miejscowo stosowanym 40% kremem z mocznikiem w monoterapii w odneisieniu do terapii łączonej.
Materiał i metody: Do badań zakwalifikowano 55 pacjentów, leczonych w poradni przyklinicznej, w ciągu 6 miesięcy. Badanie miało charakter otwarty, prospektywny, obserwacyjny i porównawczy. We wszystkich przypadkach rozpoznanie grzybicy paznokci z towarzyszącą grzybicą skóry było potwierdzone bezpośrednim badaniem mikologicznym i hodowlą. Tylko 40 chorych w pełni zakończyło udział w badaniu wraz z kontrolą w 24. tygodniu. Wyniki były analizowane na podstawie obrazu klinicznego i mikologicznego po 12 tygodniach od zakończenia 3-miesięcznej terapii. Test chi-kwadrat był wykorzystany do opracowań statystycznych.

Wyniki: Wyleczenie kliniczne oceniane w 24. tygodniu od rozpoczęcia badania uzyskano u 50% chorych leczonych terapią łączoną, natomiast w przypadku monoterapii: u 42% leczonych doustną terbinafiną, oraz u 7% chorych, którzy miejscowo stosowali 40% kremem z mocznikiem. Mikologiczne wyleczenie uzyskano w odpowiednich grupach: 93%, 67% i 14%.
Wnioski: Terapia łączona polegająca na stosowaniu doustnej terbinafiny wraz z 40% krem z mocznikiem w okluzji jest bardziej skuteczna w porównaniu z obiema monoterapiami.

Słowa kluczowe: grzybica paznokci, grzybica skóry, *Trichophyton rubrum*, *Trichophyton mentagrophytes*, terbinafina, mocznik

Introduction

Dermatophytes are parasitic fungi of keratin classified in three anamorphic genera: *Trichophyton, Microsporum* and *Epidermophyton* [1]. *Trichophyton rubrum* and *Trichophyton mentagrophytes* are the most frequent agents of onychomycosis. Hyaline and septated hyphae are observed in direct examination of scales [2]. In most cases nail affection is performed through the hyponychium, invading the matrix and the ungual plate [1].

In 2011, Hay and Baran proposed a classification of onychomycosis with 7 clinical forms:

a) Distal and lateral subungual onychomycosis
b) Superficial white or black onychomycosis
c) Proximal subungual onychomycosis (striated or secondary to paronychia)
d) Endonyx
e) Mixed (two patterns of infection)
f) Total dystrophic onychomycosis
g) Secondary onychomycosis (psoriasis, trauma, etc.) [3].

Prevalence of onychomycosis in England is of 2.7%, while in Finland and United States ranged from 7 to 10% [4-6].

Therapeutic management of onychomycosis represents a great challenge, sometimes due in part to the presence of large masses of fungal hyphae and spores. In 1962 Grimmer designated these masses as the cause of resistance to griseofulvine treatment and named them "glacier nail" [7]. Roberts and Evans renamed them as "subungual dermatophytoma" [8]. Clinically they are seen as a rounded or linear yellowish-white dense area. Fungi in these masses form a biofilm by extracellular polysaccharides, evading drugs action and decreasing the growth rate of the microorganism [9].

These fungal aggregates represent a problem for current treatments because they cannot be eliminated by antifungal drugs such as azoles and allylamines. Topical monotherapy provides poor results except on superficial white onychomycosis [10].

The increasing resistance to current treatments in onychomycosis has prompted researchers to study microorganisms and host factors, leading to the discovery of biofilms which cause chronicity and recurrence. Much has been written about combined therapy to improve efficacy and decrease the time of treatment in patients not responding to standard regimens with a single drug. However there are few studies about treatment in patients with onychomycosis and dermatophytoma.

Material and methods

We studied a total of 55 patients in a six months period, who attended the outpatient dermatology clinic from July to December 2009. An open, prospective, longitudinal and comparative study was performed. All patients with onychomycosis and dermatophytoma of toenails were confirmed by potassium hydroxide (KOH) and mycological culture. Patients who voluntary participated signed an informed consent. 40 patients completed the study and the follow-up and 15 were left out.

Randomization was performed using probabilistic method to reduce bias. A code was assigned to each patient. 14 patients received terbinafine, 250 mg/day/12 weeks plus occlusive 40% urea cream at night for 4 weeks; 12 patients were treated with occlusive 40% urea cream for 4 weeks and 14 patients with terbinafine 250 mg/day/12 weeks. A complete clinical evaluation of the patient was made at the first appointment, choosing one nail as target for subsequent clinical and mycological evaluation. The first control study with KOH was carried out at 12 weeks of treatment, with a clinical evaluation of nail dystrophy, thickness and a photographic record.

Another mycological study was performed three months after completing the treatment to assess improvement or cure. In case of topical monotherapy, it was performed 2 months after occlusive therapy.

There is no consensus about the cure for onychomycosis. Baran et al. defined it as the disappearance of entire lesion or a residual distrophy of less than 10% of the originally affected area. Lecha defined it as disappearance of any visible change or reduction of a 95% or more of damaged nail surface [11-13]. In our study, the parameter of clinical cure was the evidence of a marked improvement of the target nail, the decrease of damage (less than 1.5 mm) and thickness (less than 0.5 mm), in addition to negative results of culture and KOH. Results were analyzed according to clinical and mycological improvement 12 weeks after completing the treatment. 14 patients were left out because of the treatment desertion and one patient due to adverse effects (dyspepsia) associated to terbinafine therapy.

Chi-square test was used for discrete variables and confidence intervals were calculated.

Results

Among 40 patients, 65% were female and 95% were from urban area. 28% were in the age group 50-60 years. 60% had a family member with onychomycosis; one patient had tinea corporis (2.5%) and five patients had tinea pedis (12.5%). 3 patients (7.5%) reported diabetes mellitus and two patients (5%) systemic arterial hypertension.

14 patients (35%) had less than a year history, 14 (35%) 1 to 5 years, 3 patients – 20 years, with a mean time of 5.3 years. 22.4% of the patients had received treatment, 18% of these patients received systemic medication, one patient was treated with two systemic drugs without improvement.

21 patients had total dystrophic onychomycosis (TDO) (52.5%). 22 patients (55%) had 1 to 3 affected nails and only 6 patients (15%) more than 7 affected nails.

Trichophyton rubrum was found in 26 patients (65%), *Trichophyton mentagrophytes* in 2 patients (5%) and culture was negative in 12 patients (30%).

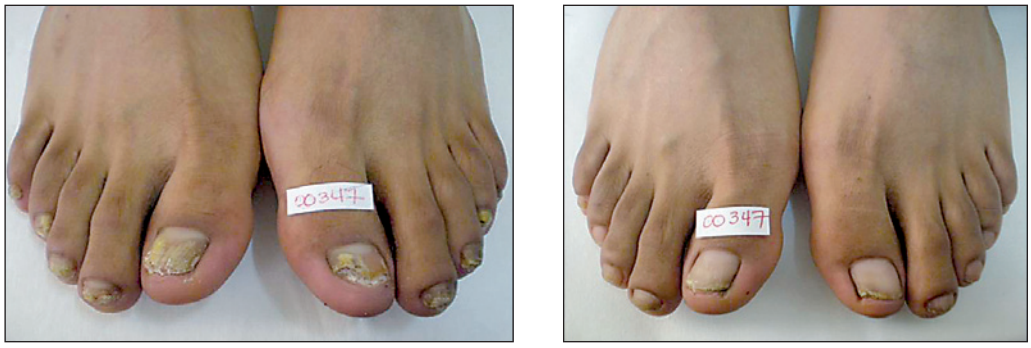
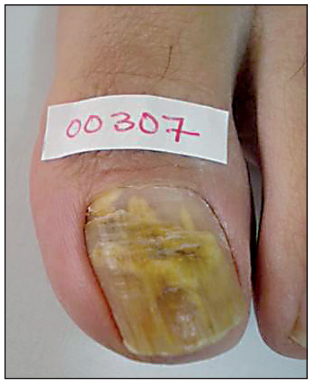


Fig. 1 and 2. Combined therapy. Oral terbinafine + oclussive 40% urea cream (week 0 and alter 24 weeks, respectively)
Ryc. 1 i 2. Terapia łączona. Doustna terbinafina + 40% krem z mocznikiem w okluzji (tydzień 0 i 24)

Table I: Comparison of KOH mycological reports at 0, 16 and 24 weeks of treatment initiation
Tabela I: Porównanie wyników bezpośrednich badań mikologicznych (KOH) po 0, 16 i 24 tygodniach leczenia

	Terbinafine + urea *Terbinafina + mocznik*			Terbinafine *Terbinafina*			40% urea *40% mocznik*		
KOH	Week *Tydzień 0*	Week Tydzień 16	Week *Tydzień 24*	Week *Tydzień* 0	Week *Tydzień 16*	Week *Tydzień 24*	Week *Tydzień 0*	Week *Tydzień 16*	Week *Tydzień 24*
Dermatophytoma	14	1	0	12	5	0	14	1	2
Dissociated / *Rozsiana postać*	0	2	0	0	0	0	0	0	0
Filaments + / *Filamenty*	0	3	1	0	6	4	0	11	9
Negative / *Wynik ujemny*	0	8	13	0	1	8	0	2	3
Total / *Ogółem*	14	14	14	12	12	12	14	14	14



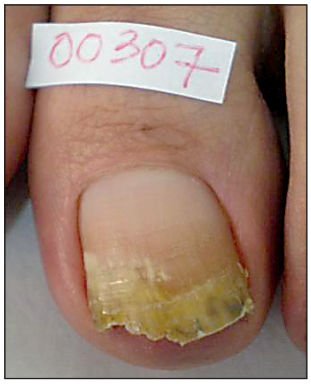
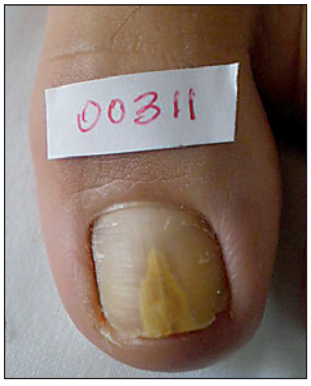


Fig. 3 and 4. Oral terbinafine treatment. Week 0 and after 24 weeks
Ryc. 3 i 4. Doustna terbinafina. Tydzień 0 i 24



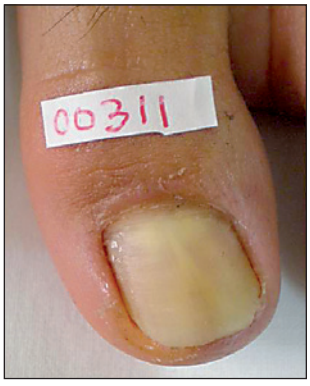


Fig. 5 and 6. 40% urea under oclussion. Week 0 and after 24 weeks
Ryc. 5 i 6. 40% krem z mocznikiem w okluzji. Tydzień 0 i 24

Mycological evaluation with KOH after 12 weeks of combined treatment was negative in 57% and in only 8% with terbinafine monotherapy (fig. 1-2, tab. I). Mycological cure with combined therapy occurred in 92.8%, statistically significant with a confidence interval of 95% (fig. 3-4). Monotherapy with occlusive 40% urea cream at 12 week, showed hyphae at mycological evaluation with KOH in 11 of 12 patients of this group; 3 patients had negative culture at week 24 but in 2 patients it persisted with the dermatophytomas (fig. 5-6).

Mycological culture was positive in 72.5% of cases and 12 weeks after completing the treatment in 30%.

Based on these data and the calculation of confidence interval for clinical and mycological cure, in the 24th week seven patients (50%) obtained complete cure in the group of combined therapy, 5 patients (43%) in the group of monotherapy with terbinafine and one patient (7%) in occlusive 40% urea group.

Side effects: 3 patients (11%) presented excessive periungual maceration because of occlusive urea, however none discontinued treatment. In the combined therapy group, one patient (2.5%) had onychomadesis at 8th week of treatment. 2 patients (7%), one of each group of monotherapy, presented onychocryptosis at 12th week of treatment. One of these patients developed a transverse band of leukonychia secondary to the use of occlusive urea but then improved at 24th week. The onychogryphosis ameliorated in one patient (2.5%) after treatment with terbinafine monotherapy. Only one patient (2.5%) showed deterioration extending from 3 to 5 affected nails in the group of monotherapy with 40% urea cream. One patient of terbinafine monotherapy was excluded because of gastritis as an adverse effect.

Discussion

There are few epidemiological studies that indicate the frequency of dermatophytomas. In a previous publication (Martínez, JAAD) 7 cases were reported in 793 patients with subungual onychomycosis; in this report the frequency was low. Another study in Guatemala reported 5.3% of dermatophytomas in 100 cases during a year [14].

In our study, women with onychomycosis were predominant in contrast to the literature which states that the highest rates of ony-

chomycosis are associated to men. This result may be due to the fact that women seek consults more than men; or for aesthetic reasons. We agree with Nelson et al. [15] about the age groups, who mentioned that the condition mostly affects the adult population between the 3rd and 6th decades [16, 17].

We found only 6 patients with concomitant superficial fungal infections. Systemic arterial hypertension and diabetes mellitus have been described as predisposing factors due to inadequate perfusion of ungula matrix leading to local immunosuppression [18].

Both recurrence and reinfection of onychomycosis are common, mainly by previous insufficient or inadequate treatments as was in 40.5% of the patients [19].

The totally dystrophic onychomycosis (TDO) was the most frequent clinical form, seen in 21 patients (52.5%). This coincide with Sommer et al. studies [20] where it was reported in 46% of patients in England. Nevertheless distal and lateral subungual onychomycosis (DLSO) occurs in a higher percentage (54%).

The main etiologic agent was *Trichophyton rubrum* (65%), followed by *Trichophyton mentagrophytes* (5%), according with most papers in the literature [7, 18, 19, 21, 22]. The persistence of two positive cultures for *Trichophyton mentagrophytes* which proceeds the previously growth of *Trichophyton rubrum* is due probably to an initial mixed infection. Piraccini et al. also mentioned distinct subspecies in subsequent cultures [18].

It has been mentioned that dermatophytoma must be treated with chemical nail avulsion of 1% bifonazole and 40% urea without studies that supports the best treatment [23].

12 weeks after completing the treatment, a negative culture was reported in 8 patients (66.6%) of monotherapy with terbinafine, in 3 patients (21.4%) of the urea monotherapy group and in 13 patients (92.8%) of the combined therapy (tab. I), being statistically significant according to 95% confidence interval.

Our study shows that combined therapy has a significant clinical improvement compared to monotherapy. This could be synergistic action of both drugs [23]. Fräki J. et al. in an open multicentric study conducted in 1997, demonstrated significant improvement with combined therapy of fluconazole and urea ointment [24].

Conclusions

Subungual dermatophytomas are masses of fungal hyphae and spores [7] protected by biofilms formed by extracellular polysaccharides synthesized by bacteria or fungi [9] and represent a problem for current treatments.

Combination therapy of oral terbinafine and 40% urea cream is more effective than monotherapy of both for the treatment of onychomycosis with dermatophytoma. There was no significant difference with terbinafine monotherapy, however it was greater comparing to the 40% urea cream.

References

1. Arenas R. *Dermatología. Atlas, Diagnóstico y Tratamiento 5ta*. ed. Mexico DF. McGraw Hill Companies. 2012. p.478-489.
2. De Vroey C. *Epidemiology of ringworm (dermatophytosis).* Semin Dermatol. 1985;4:185-200.
3. Hay RJ, Baran R. *Onychomycosis: A proposed revision of the clinical classification*. J Am Acad Dermatol 2011;65:1219-1227.
4. Roberts DT. *Prevalence of dermatophyte onychomycosis in the United Kingdom: Results of an omnibus survey.* Br J Dermatol. 1992;126:23-27.
5. Heikkilå H, Stubb S. *The prevalence of onychomycosis in Finland*. Br J Dermatol. 2006;133:699-703.
6. Elewski BE, Charif MA. *Prevalence of onychomycosis in patients attending a dermatology clinic in northeastern Ohio for other conditions.* Arch Dermatol. 1997;133:1172-1173.
7. Seebacher C, Brasch J, Abeck D, et al. *Onychomycosis.* Mycoses. 2007;50: 321-327.
8. Roberts, Evans. *Subungual dermatophytoma complicating dermatophyte onychomycosis.* Br J Dermatol. 1998;138:189-190.
9. Burkhart CN, Burkhart CG, Gupta AK. *Dermatophytoma: Recalcitrance to treatment because of existence of fungal biofilm*. J Am Acad Dermatol. 2002;47:629-631.
10. Del Palacio A, Garau M, Cuétara MS. *Current treatment of dermatophytosis*. Rev Iberoam Micol. 2002;19:68-71.
11. Zaug M, Bergstraesser M. *Amorolfine in the treatment of onychomycoses and dermatomycoses (an overview).* Clin Exp Dermatol. 1992;17(Suppl 1): 61-70.
12. Baran R, Kaoukhov A. *Topical antifungal drugs for the treatment of onychomycosis: an overview of current strategies for monotherapy and combination therapy.* J Eur Acad Dermatol Venereol. 2005;19:21-29.
13. Lecha M, Effendy I, Feuilhade de Chauvin M, et al. *Treatment options--development of consensus guidelines*. J Eur Acad Dermatol Venereol. 2005;19 Suppl 1:25-33.
14. Martínez E, Alas Carbajal R, Escalante K, et al. *Dermatofitoma subungueal. Estudio epidemiológico de 100 casos en Guatemala.* Rev Chil Dermatol. 2010;26:22-24.
15. Nelson MM, Martin AG, Heffernan MP. *Superficial Fungal Infections. In: Fitzpatrick's Dermatology in General Medicine.* 7th. Ed. New York. McGraw Hill. 2008. Section 30. p.1807-1821.
16. Organización Panamericana de la Salud. Perfil del Sistema de Salud de Guatemala. Washington DC. Informe de grupo científico de la OPS. Washington DC: OPS; 2007. Serie de informes técnicos NLM WA 525.
17. Instituto Nacional de Estadística. Encuesta Nacional de Condiciones de Vida Perfil del Sistema de Salud de Guatemala. Guatemala: ENCOVI 2000. Serie de informes técnicos GTM_2000_ENCOVI_v01_M.
18. Gupta AK, Tu LQ. *Onychomycosis therapies: strategies to improve efficacy*. Dermatol Clin. 2006;24:381-386.
19. Sigurgeirsson B, Olafsson JH, Steinsson JB, et al. *Long-term effectiveness of treatment with terbinafine vs itraconazole in onychomycosis: a 5-year blinded prospective follow-up study.* Arch Dermatol. 2002;138:353-357.
20. Sommer S, Sheehan-Dare RA, Goodfield MJD, Evans EGV. *Prediction of outcome in the treatment of onychomycosis*. Clin Exp Dermatol. 2003;28:425-428.
21. Gupta M, Sharma NL, Kanga AK, et al. *Onychomycosis: Clinico-mycologic study of 130 patients from Himachal Pradesh, India*. Indian J Dermatol Venereol Leprol. 2007;73:389-392.
22. Roberts DT, Taylor WD, Boyle J. *Guidelines for treatment of onychomycosis*. Br J Dermatol. 2003;148:402-410.
23. Martínez Herrera E, Moreno Coutiño G, Fernández Martínez R, et al. *Case Letter. Dermatophytoma: Description of 7 cases*. J Am Acad Dermatol. 2012;66:1014-1016.
24. Fräki J, Heikkila H, Kero M, et al. *An opel-label, noncomparative, multicenter evaluation of Fluconazole with or without urea nail pedicure for treatment of onychomycosis*. Curr Therap Res. 1997;58:481-491.

Received: 2013.05.13. Approved: 2013.06.19.

Conflict of interests: none declared

Address for correspondence:
Professor Roberto Arenas, MD
Mycology Section, 'Dr. Manuel Gea González' General Hospital
Mexico City, Mexico
e-mail: rarenas98@hotmail.com