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A Retrospective Study Comparing K101 Nail Solution as a Monotherapy and in Combination with Oral Terbinafine or Itraconazole for the Treatment of Toenail Onychomycosis

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Keywords
Tinea unguium · Topical therapy · Fungal infection

Abstract
Background: Onychomycosis is a difficult-to-treat fungal infection of the nails. The efficacy of monotherapy is not ideal, and combination therapies provide an alternative that may increase treatment efficacy. ***Method:*** A retrospective analysis of data from 91 patients was undertaken. Treatment for toenail onychomycosis occurred between 2014 and 2016 and consisted of combination therapy with oral terbinafine (250 mg/day for 12 weeks) or itraconazole (3 pulses, 400 mg/day for 7 days) + K101 nail solution daily, or K101 nail solution monotherapy. Efficacy outcomes at 12 and 15 months were analyzed. ***Results:*** At 12 months, the clinical cure rate for combination of terbinafine + K101 solution was significantly higher than that for K101 monotherapy ($p = 0.008$). Patients receiving this combination also showed significant improvement in percent of affected nail at 3 months ($p = 0.029$), while patients receiving itraconazole + K101 solution demonstrated improvement in percent of affected nail at 6 months ($p = 0.037$). At 15 months, there was no significant difference between treatments for complete, clinical, and mycological cure. ***Conclusion:*** Combination therapy with oral terbinafine or itraconazole and K101 nail solution results in clearance of infected nail earlier than that with topical K101 alone. These combinations may encourage compliance and be effective for patients with moderate onychomycosis.

Introduction

Onychomycosis is a fungal infection of the nails that is characterized by discoloration, nail plate thickening, and onycholysis [1]. The efficacy of oral antifungal treatments ranges from 38 to 75% for mycological cure and from 23 to 46% for complete cure [2]. Topical antifungal treat-

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Table 1. Baseline participant characteristics

		Treatment arms			Total	*p* values
		K101	T + K101	I + K101		
Gender	males	25	22	7	54 (59.3%)	0.507
	females	19	11	7	37 (40.7%)	
	total	44	33	14	91	
Mean age ± SD, years		43.8±9.3	44.7±11.6	41.6±7.0	43.9±9.8	0.624
Disease duration	<10 years	7	6	3	16 (17.6%)	0.776
	10–19 years	19	18	6	43 (47.3%)	
	≥20 years	18	9	5	32 (35.2%)	
	total	44	33	14	91	
BL severity (% nail involvement)	31–49%	36	27	13	76 (83.5%)	0.592
	≥50%	8	6	1	15 (16.5%)	
	total	44	33	14	91	
BL culture	dermatophyte	33	24	12	69 (75.8%)	0.731
	Candida spp.	1	3	0	4 (4.4%)	
	NDM	4	1	1	6 (6.6%)	
	mixed infection	6	5	1	12 (13.2%)	
	total	44	33	14	91	

T, terbinafine; I, itraconazole; SD, standard deviation; BL, baseline; NDM, nondermatophyte.

ments may be preferred for patients with mild disease or those who are immunocompromised or using multiple medications. However, the efficacy of topical antifungals ranges from 29 to 90% for mycological cure and from 1 to 18% for complete cure [3].

Combining oral and topical antifungal regimens could potentially increase cure rates for onychomycosis. Whereas mild cases (<30% diseased nail) of onychomycosis may not benefit significantly more from combination treatment, evidence suggests that moderate to severe cases of onychomycosis, or cases with traditionally difficult-to-treat features (e.g., dermatophytoma, onycholysis), could benefit from combination treatment [4–6]. Combination therapies that have shown efficacy in treating onychomycosis include oral terbinafine with topical amorolfine [5, 6] or ciclopirox [6, 7], and itraconazole with amorolfine [8].

K101 nail solution (Emtrix®, Kerasal Nail®, Nalox™/Naloc™) is available without prescription and is marketed in the EU, Asia, and North America as a treatment for onychomycosis. This nail solution is a combination of propylene glycol (66.4%), urea (20%), and lactic acid (10%), which likely act in combination to produce keratolytic, softening, and antimycotic effects. A randomized double-blind controlled trial reported mycological cure rates with K101 solution that were similar to those reported for ciclopirox and amorolfine lacquers [3]. Patients also reported improvement of clinical symptoms, such as thickening, discoloration, and brittleness of nails [9].

The current study is a retrospective analysis of patients undergoing treatment for toenail onychomycosis. We compared combination treatment of oral terbinafine or itraconazole and topical K101 nail solution with K101 nail solution monotherapy.

Methods

This was a retrospective analysis of data from 91 patients with toenail onychomycosis undergoing treatment between May 2014 and March 2016, and, as such, the analysis did not require institutional approval. Patients were diagnosed with mycologically confirmed (positive smear and positive culture) distal lateral subungual onychomycosis of the great toenail, with up to 75% baseline nail involvement. Mycology was performed at a government-approved mycology laboratory associated with a dermatology practice. To determine the causative organism, nondermatophyte

Table 2. Organisms cultured at baseline

Organism(s)	Treatment arm		
	K101	T + K101	I + K101
Dermatophytes			
Trichophyton rubrum	29	16	11
Trichophyton mentagrophytes	3	6	
Trichophyton tonsurans	1	1	
Epidermophyton floccosum		1	1
Nondermatophytes			
Acremonium spp.	2		1
Fusarium spp.	1		
Penicillium spp.	1		
Scopulariopsis spp.		1	
Candida			
Candida albicans		2	
Candida krusei		1	
Candida tropicalis	1		
Mixed infections			
T. rubrum + *Acremonium*	1		1
T. mentagrophytes + *C. krusei*		1	
T. rubrum + *Neoscytalidium dimidiatum*	2	1	
T. rubrum + *Fusarium*	2	1	
T. mentagrophytes + *Penicillium*	1	2	

T, terbinafine; I, itraconazole.

mold or *Candida* spp. were required to be cultured 3 times in the absence of dermatophytes [10]. The amount of infected and healthy nail was measured longitudinally in mm at baseline and at subsequent visits.

All patients ($n = 91$) used topical K101 nail solution once daily for 15 months. Treatment consisted of topical therapy alone ($n = 44$) or of topical therapy in parallel with either oral terbinafine, 250 mg once daily for 12 weeks ($n = 33$), or 3 pulses of itraconazole, 200 mg twice daily for 7 days ($n = 14$). Follow-up visits took place at 3, 6, 12, and 15 months, with mycological samples taken at 15 months (smear and culture).

Efficacy outcomes evaluated in this study included clinical cure, mycological cure, and complete cure. Clinical cure was defined as 100% clear nail, evaluated at 12 and 15 months. Mycological cure was defined as negative smear and negative culture, and complete cure was defined as 100% clear nail with mycological cure, both evaluated at 15 months. The proportion of affected nail was calculated at all visits. Categorical baseline participant variables and efficacy outcomes were compared with χ^2 and Fisher exact tests, while continuous baseline participant variables were compared using one-way ANOVA. A mixed linear model was used to compare percent clear nail between treatments and across visits, and Bonferroni correction was used for comparisons. Significance was set to $\alpha = 0.05$.

Results

The mean age of this sample was 43.8 ± 9.9 years, with 59% of patients being male. The majority of patients were aged 59 years or younger, with 38.5% under the age of 40 years and 52.7% between ages 40 and 59 years. Onychomycosis had been present for 10 years or longer in 83% of the patients. Patients clinically presented with onychomycosis affecting between 31 and 60% of the nail (Table 1). Culture was obtained at baseline prior to treatment. Dermatophyte, mixed dermatophyte-nondermatophyte mold, nondermatophyte mold, and *Candida* infections comprised 75.8, 13.2, 6.6, and 4.4% of the sample, respectively (Tables 1, 2). There were no significant differences in baseline characteristics between the treatment groups ($p_s > 0.05$; Table 1).

Analysis of percent of affected nail across time produced a significant time × treatment interaction ($F(8, 401) = 2.48$, $p = 0.012$). All 3 treatments produced significant improvements from baseline in percent of nail affected ($p < 0.001$). At 3 ($p = 0.001$), 6 ($p < 0.001$), 12 ($p < 0.001$), and 15 months ($p = 0.021$), the percent of affected nail for the combination of terbinafine + K101 was significantly lower than that for K101 topical solution alone. The combination of itraconazole + K101 also showed significant improvement compared to K101 topical solution alone at both 6 ($p = 0.037$) and 12 months ($p = 0.008$).

Table 3 shows efficacy outcomes at 12 and 15 months. After 12 months of topical treatment with K101, those patients who also had oral terbinafine demonstrated a clinical cure rate that was significantly higher than that with K101 treatment alone (42.4 vs. 9.1%, $p = 0.003$). The efficacy rate of itraconazole combined with K101 was not significantly different from either group. At 15 months, there were no differences in efficacy rates between treatments for clinical, complete, and mycological cure ($p_s > 0.05$). χ^2 tests were also conducted on dermatophyte-only infections (Table 3) with the same patterns observed. Omitting *Candida* infections from the analyses did not alter the findings.

Discussion

K101 topical nail solution monotherapy was compared to K101 solution in combination with oral terbinafine or itraconazole. Combination treatments did not produce significantly higher cure rates at 15 months. However, cure rates were qualitatively higher with both

Table 3. Efficacy outcomes stratified by organism cultured at baseline

	Organism	12 months	15 months		
		clinical cure	complete cure	clinical cure	mycological cure
K101	total	4/44 (9.1%)	13/44 (29.5%)	13/44 (29.5%)	24/44 (54.5%)
	derm.	4/33 (12.1%)	11/33 (33.3%)	11/33 (33.3%)	16/33 (48.5%)
	NDM	0/4	0/4	0/4	3/4
	Candida	0/1	1/1	1/1	1/1
	mixed	0/6	1/6	1/6	4/6
Terbinafine + K101	total	14/33 (42.4%)*	18/33 (54.5%)	18/33 (54.5%)	21/33 (63.6%)
	derm.	10/24 (41.7%)*	14/24 (58.3%)	14/24 (58.3%)	15/24 (62.5%)
	NDM	0/1	1/1	1/1	1/1
	Candida	1/3	1/3	1/3	2/3
	mixed	3/5	2/5	2/5	3/5
Itraconazole + K101	total	5/14 (35.7%)	9/14 (64.3%)	9/14 (64.3%)	10/14 (71.4%)
	derm.	4/12 (33.3%)	8/12 (66.7%)	8/12 (66.7%)	8/12 (66.7%)
	NDM	0/1	1/1	1/1	1/1
	mixed	1/1	0/1	0/1	1/1

Derm., dermatophyte; NDM, nondermatophyte. * $p < 0.05$, terbinafine + K101 significantly different from K101 alone.

combination treatments. Additionally, evidence of successful treatment was observed much earlier in time with the combination of oral terbinafine and K101 nail solution compared to monotherapy; as early as 3 months into treatment. Combinations can take advantage of the multiple routes by which antifungal agents reach the site of fungal nail infections [11]. This may be relevant for patients who can tolerate oral treatment, as a reduction in clinical signs and symptoms can encourage treatment compliance.

Efficacy rates in the current sample are consistent with published results. Previously, mycological cure after K101 treatment for 6 months was 27.2% (dermatophyte-confirmed onychomycosis with ≤50% of nail involvement), while patient-rated reduction or patient-rated absence of symptoms was reported by 42.9% [12]. The current study included patients with up to 75% of nail involvement; complete and mycological cure of dermatophyte infections after 15 months of K101 solution alone were 33.3 and 48.5%, respectively. Combination treatment with oral terbinafine or itraconazole and K101 nail solution produced complete cure rates at 15 months (54.5 and 64.3%, respectively) similar to the success rate of 59.2% (negative mycology and ≤10% of original total diseased nail still affected) reported at 18 months with oral terbinafine and amorolfine [5].

This sample included patients with nondermatophyte and mixed infections. Clinical trials usually enroll dermatophyte-confirmed onychomycosis, yet recent epidemiological studies have reported a prevalence of nondermatophyte/mixed infections ranging from 28 to 48% [13, 14]. Although the present study included few patients with these infections (n = 18), mycological cure was observed in 13 patients.

There are limitations to this study. The retrospective nature and small sample size of the current analysis prevent generalization of the results. Additionally, oral antifungal monotherapy was not included, and it is possible that the efficacy of the combination groups reflects oral treatment alone. However, these data demonstrate that combination treatment of terbinafine or itraconazole with K101 nail solution may be effective for patients with moderate onychomycosis. The clearance of affected nail observed at 3 and 6 months with combination treatment may encourage patient compliance compared to monotherapy. The future in treating onychomycosis likely entails finding successful combinations of antifungal treatments or combinations of antifungal treatments in concert with devices.

Statement of Ethics

This was a retrospective analysis of data from 91 patients, and, as such, the analysis did not require institutional approval.

Disclosure Statement

The authors have nothing to disclose.

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