Original Article

Effectiveness and safety of topical amphotericin B in 30% dimethyl sulfoxide cream versus 30% dimethyl sulfoxide cream for nondermatophyte onychomycosis treatment: A pilot study

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Abstract

Background: Although topical amphotericin B cream is effective for the treatment of nondermatophyte mold onychomycosis *in vitro*, studies of its effectiveness and safety *in vivo* are limited.

Objectives: We studied the effectiveness and safety of topical 0.3% amphotericin B in 30% dimethyl sulfoxide cream (amphotericin B cream) in nondermatophyte mold onychomycosis using the vehicle cream 30% dimethyl sulfoxide cream as control.

Methods: This randomized controlled study was conducted between January 2019 and November 2020. Patients diagnosed with nondermatophyte mold onychomycosis were randomly divided into two groups of ten patients each: one treated with amphotericin B cream and the other with the vehicle cream. Clinical and mycological cure as well as safety were evaluated.

Results: Ten patients each treated with amphotericin B cream and the vehicle cream were included in the study, but only nine patients in the vehicle cream group were available for follow up. All the 19 evaluable patients had distal lateral subungual onychomycosis and the great toenails were affected in 18 (94.7%) of these. Mycological cure was achieved in 8 (80%) patients treated with amphotericin B cream and in 4 (44.4%) patients using the control (vehicle) cream. Clinical cure was achieved in 7 (70%) patients treated with amphotericin B cream, but only in 2 (22.2%) patients on the control cream. No adverse events were observed.

Limitations: The small sample size and the fact that PCR fungal identification that provides accurate identification of fungal species was not performed are limitations of our study.

Conclusion: Topical amphotericin B cream was both very effective and safe in the treatment nondermatophyte mold onychomycosis. The control (vehicle) cream containing 30% dimethyl sulfoxide also demonstrated some antifungal activity.

Key words: amphotericin B, dimethyl sulfoxide, fungi, onychomycosis, topical

Plain Language Summary

Onychomycosis is a fungal infection of the nail caused by dermatophytes, nondermatophyte molds (NDMs), and yeasts. Currently, the incidence of nondermatophyte mold onychomycosis is increasing affecting 24 to 50% of the population. However, the most effective treatment for it is limited. Topical amphotericin B is an antifungal drug that has been found to be effective for the treatment of nondermatophyte mold onychomycosis in laboratories. Nonetheless, studies on its effectiveness and safety in patients are limited. The researchers, from the Thailand, aimed to investigate the effectiveness and safety of topical 0.3% amphotericin B in 30% dimethyl sulfoxide (DMSO) cream and 30% DMSO cream in treating onychomycosis caused by nondermatophyte molds. Patients diagnosed with nondermatophyte mold onychomycosis were divided into

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two groups including 0.3% amphotericin B in 30% DMSO cream and 30% DMSO cream (10 patients/group). Treatment responses which include 'clinical cure' (>95% visible clearing of the nail), 'mycological cure' (the fungus has been killed), and safety were evaluated. Their findings showed that the clinical cure rate for 0.3% amphotericin B in 30% DMSO cream was higher than that for 30% DMSO cream (70% vs 22%), while mycological cure was achieved in 80% and 44% of the patients treated with 0.3% amphotericin B in 30% DMSO cream and 30% DMSO cream, respectively. No side effects were reported during the study period. The authors concluded that topical 0.3% amphotericin B in 30% DMSO cream showed excellent effectiveness and safety for the treatment of nondermatophyte mold onychomycosis.

Introduction

Onychomycosis is a common problem caused by dermatophytes, nondermatophyte molds and yeasts.[1] The prevalence of nondermatophyte mold onychomycosis is increasing, especially in tropical countries with reported prevalence rates of 24.1% to 51.6%.[2-5] The most common nondermatophyte molds isolated are *Scopulariopsis brevicaulis*, *Fusarium* species, *Aspergillus* species, *Neoscytalidium dimidiatum* and *Acremonium* species,[6] with *Neoscytalidium dimidiatum* being the most prevalent organism in Thailand.[4,7]

Treatment modalities for nondermatophyte mold onychomycosis include the use of oral and topical antifungal drugs, and either chemical or surgical nail avulsion.[1,6,8-11] Amphotericin B is an antifungal from the polyene class of antimicrobial compounds with broad fungicidal properties and a low rate of resistance.[12] It binds to ergosterol in the fungal cell membrane forming permeable channels resulting in the leakage of ions and metabolites, thus causing cell death.[16-18] Topical amphotericin B been found to be efficacious *in vitro* against nondermatophyte molds with minimum inhibitory concentrations ranging from 0.06 to 1 μg/ml.[5,13-15] As it is highly lipophilic, a drug delivery vehicle such as dimethyl sulfoxide is often used to enhance its therapeutic effect.[19]

Dimethyl sulfoxide is a stable, highly polar, water-soluble compound with antifungal properties, frequently used as a solvent to the enhance penetration of antifungal drugs. [20,21] An extemporaneous ointment preparation of amphotericin B in 30% dimethyl sulfoxide was shown to achieve concentrations well above the minimum inhibitory concentrations for nondermatophyte molds *in vitro* in a nail model.[22] However, published *in vivo* studies of topical amphotericin B for this condition have been few. In this study we report the effectiveness and safety of topical amphotericin B in 30% dimethyl sulfoxide in nondermatophyte mold onychomycosis treatment.

Materials and Methods

Study design

This randomized, double-blind clinical trial was conducted at the Nail Clinic, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand, between January 2019 and November 2020. The trial was registered with ClinicalTrials.gov (NCT03814343) and the study protocol was approved by Siriraj Institutional Review Board (no. Si 799/2018). All patients provided signed informed consent. Patients were assigned to two groups using mixed-blocked randomization. The first group received topical amphotericin B cream while the second received the vehicle cream.

Subjects

Twenty patients with nondermatophyte mold onychomycosis were enrolled and randomized into two groups of ten each. All patients were over 18 years of age and none had been treated with oral, topical or intravenous antifungal therapies during the preceding 36 weeks. Patients with dermatophyte onychomycosis, mixed onychomycosis or other concomitant nail diseases (such as psoriatic nail or paronychia) and immunocompromised patients were excluded.

Nondermatophyte mold onychomycosis was diagnosed as per the criteria of Gupta *et al*. which included positive microscopic examination of nail clippings in 20% potassium hydroxide solution, isolation of nondermatophyte molds on at least two occasions on fungal culture from repeated samplings, exclusion of dermatophytes and histological examination.[6]

Preparation of medication

Amphotericin B (Amphotret, Bharat Serums and Vaccines Ltd., New Delhi, India) was mixed with 30% dimethyl sulfoxide cream (Emplura, Merck, Kenilworth, N.J., USA) to achieve the desired amphotericin B concentration of 3 mg/ml. The 30% dimethyl sulfoxide cream served as control. Both the preparations were stored in identical aluminum tubes at temperatures ranging from 2°C to 8°C.

Patients were instructed to apply a pea-sized amount of cream once daily before bedtime to the affected nails and to wrap them in tape overnight to enhance penetration of the medication. No other systemic antifungal agent was given during the study period.

Treatment, follow-up and measurement

Patients were directed to apply the medication continuously for 36 weeks. The clinical status, mycological test results, adherence to the drug regimen and adverse events were assessed at 0, 12, 24 and 36 weeks. Subsequent evaluations after the treatment period (clinical status, mycological test results and adverse events) were performed at 48, 60 and 72 weeks. The severity of onychomycosis was assessed based on the Onychomycosis Severity Index (OSI).[23] Clinical evaluation was performed by two treatment-blinded investigators (CL and SB); "clinical cure" was defined as >95% clinically normal. The assessment of efficacy was based on mycological tests results with "mycological cure" being defined as negative potassium hydroxide test and fungal culture results.[24]

Statistical analysis

The data were analyzed using descriptive statistics. Fisher's exact test was employed to compare the differences among the categorical variables. The continuous variables with and without normal distribution were analyzed using independent t-tests and Mann–Whitney U-tests, respectively. $P \leq 0.05$ was deemed statistically significant. Data were analyzed using PASW Statistics for Windows (version 18; SPSS Inc., Chicago, Ill., USA).

Results

A total of 20 patients with nondermatophyte mold onychomycosis were selected for the study. One of the ten patients in the control group was excluded from the analysis as she did not attend the follow-up sessions. The demographic data and clinical characteristics of these 19 patients are listed in Table 1. The mean (SD) age was 68.9 (8.6) years and 10 (52.6%) patients were male. There were no significant differences in the underlying diseases, disease duration, onychomycosis severity and predisposing factors in the two groups. All 19 patients had distal lateral subungual onychomycosis and the great toenails were affected in 18 (94.7%) of the patients. A concomitant fungal foot infection was noted in 12 (63.2%) patients. *Neoscytalidium* spp. were isolated on fungal cultures in 15 (78.9%) and Fusarium spp. in 4 (21.1%) cases. Most of the patients (18/19; 94.7%) reported good adherence to the treatment.

Clinical cure was seen in 7 of the 10 (70%) patients who received amphotericin B cream but in only 2 of 9 (22.2%) patients treated with the vehicle cream. The mycological cure rates for amphotericin B were also higher than for the vehicle cream (80% vs. 44.4%). The two mycological failures in the amphotericin B cream group had *Neoscytalidium* spp. onychomycosis. No adverse events were reported during the 72 weeks of the study in either group. Figure 1 shows representative photographs of clinical improvement in onychomycosis treated with amphotericin B cream and vehicle cream.

Discussion

There is no currently recommended standard treatment for nondermatophyte mold onychomycosis.[25] In this study we demonstrate not only the high effectiveness of amphotericin B in 30% dimethyl sulfoxide cream in nondermatophyte mold onychomycosis, but also modest effectiveness of the vehicle cream containing only 30% dimethyl sulfoxide.

Studies on the topical treatment of nondermatophyte mold onychomycosis are few. Earlier reports have noted a 44% mycological response rate with 8% ciclopirox nail lacquer in 18 patients with *Neoscytalidium* spp. onychomycosis at

Table 1: Demographic data and clinical characteristics of patients diagnosed with nondermatophyte onychomycosis

Parameters	Total (*n*, 19)	Topical amphotericin B cream (*n*, 10)	Vehicle cream (*n*, 9)	*P*-value
Sex				
Male	10 (52.6)	5 (50.0)	5 (55.6)	1.000
Female	9 (47.4)	5 (50.0)	4 (44.4)	
Age (years), mean±SD	68.9 ± 8.6	70.7±6.8	66.9±10.3	0.351
Disease duration (months), median (min, max)	41.0 (9.0,124.0)	42.5 (10.0,87.0)	41.0 (9.0,124.0)	0.191
OSI score, median (min, max)	3.0 (1.0,13.0)	1.5 (1.0,12.0)	3.0 (1.0,13.0)	0.511
Predisposing factors for onychomycosis				
Hyperhidrosis of the feet	5 (26.3)	4 (40.0)	1 (11.1)	0.303
Impaired circulation	2 (10.5)	2 (20.0)	0	0.474
History of foot trauma	7 (36.8)	4 (40.0)	3 (33.3)	1.000
History of contact with pets	7 (36.8)	3 (30.0)	4 (44.4)	0.650
Physical examination				
Most severely affected toenails				
Big toenails	18 (94.7)	9 (90.0)	9 (100.0)	1.000
Third toenails	1 (5.3)	1 (10.0)	0	
Depth of nail involvement				
<1/3	16 (84.2)	8 (80.0)	8 (88.9)	1.000
1/3–2/3	3 (15.8)	2 (20.0)	1 (11.1)	
Fungal culture results				
Neoscytalidium spp.	15 (78.9)	7 (70.0)	8 (88.9)	0.582
Fusarium spp.	4 (21.1)	3 (30.0)	1 (11.1)	
Concomitant fungal foot infection	12 (63.2)	6 (60.0)	6 (66.7)	1.000
Concurrent foot deformity	8 (42.1)	4 (40.0)	4 (44.4)	1.000
Clinical cure rate	9 (47.4)	7 (70.0)	2 (22.2)	0.070
Time to clinical cure (months), mean±SD (*n*=9)	10.6±4.6	10.4±5.3	11.0±0	0.786
Mycological cure rate	12 (63.2)	8 (80.0)	4 (44.4)	0.170
Time to mycological cure (months), mean±SD (*n*=12)	8.8±5.2	9.5±6.0	7.5±3.4	0.482

*P<0.05 indicates statistical significance. OSI: Onychomycosis severity index, SD: Standard deviation

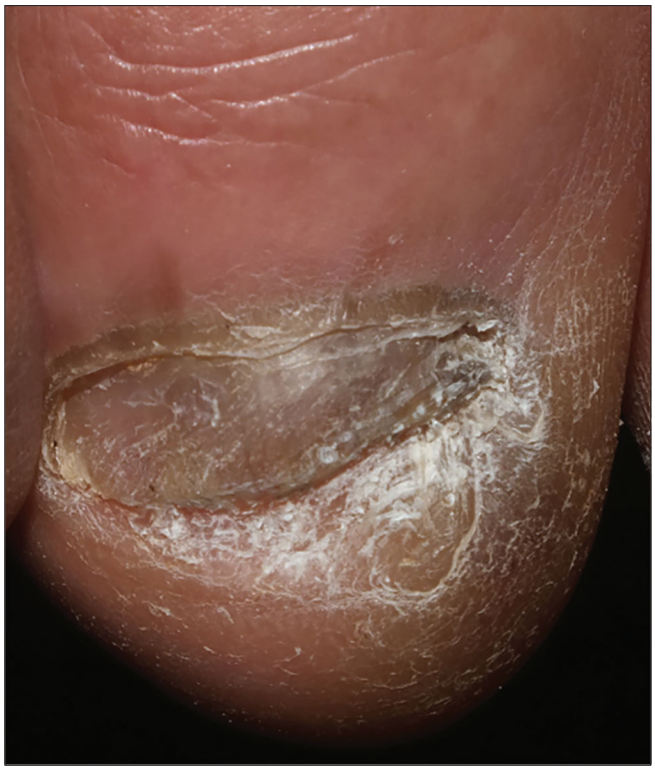

Figure 1a: Amphotericin B at baseline. Representative photographs of clinical improvement in onychomycosis treated with amphotericin B cream and vehicle cream

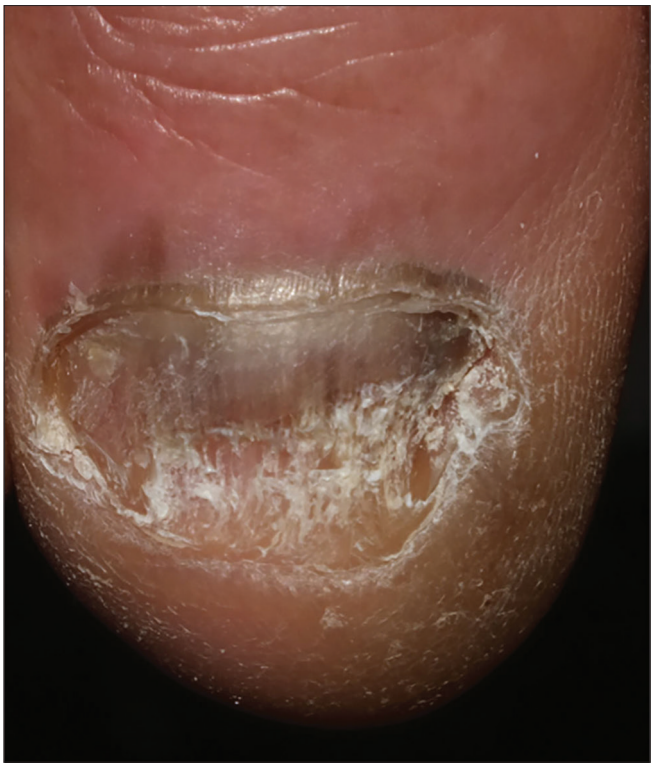

Figure 1b: Amphotericin B at 3 months. Representative photographs of clinical improvement in onychomycosis treated with amphotericin B cream and vehicle cream

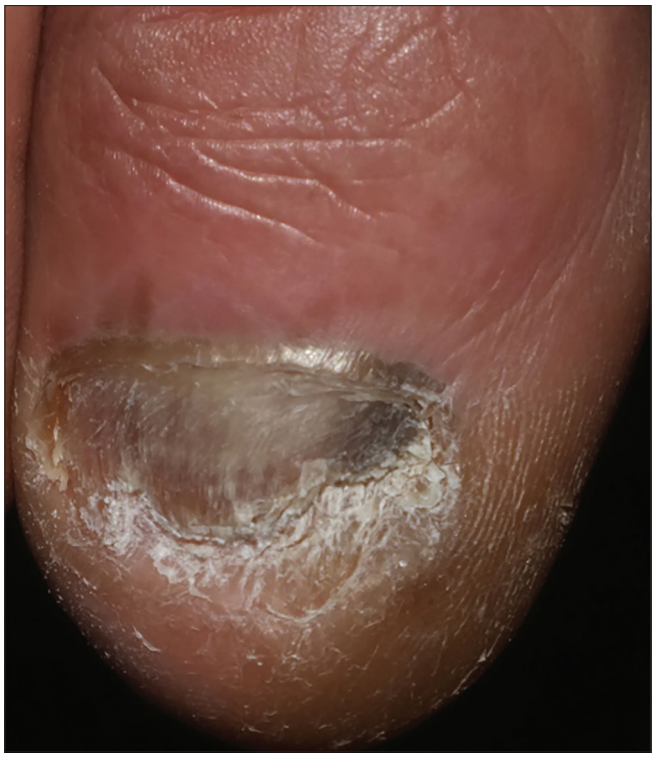

Figure 1c: Amphotericin B at 6 months. Representative photographs of clinical improvement in onychomycosis treated with amphotericin B cream and vehicle cream

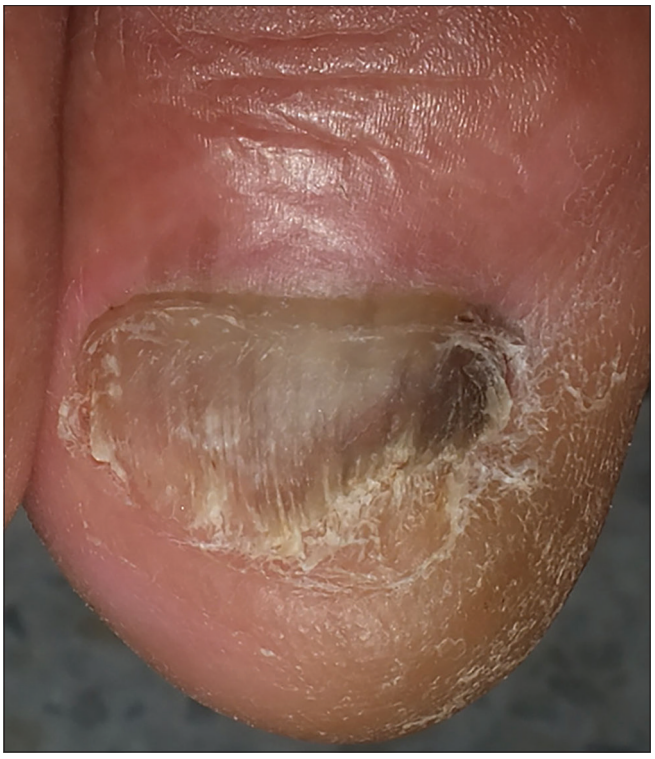

Figure 1d: Amphotericin B at 12 months. Representative photographs of clinical improvement in onychomycosis treated with amphotericin B cream and vehicle cream

12 months and 89.3% mycological cure with 5% amorolfine nail lacquer in *N. dimidiatum* onychomycosis.[25,26] In the latter study, a mycological cure of 32% was noted in those patients receiving only 40% urea cream with occlusion[26] Combined

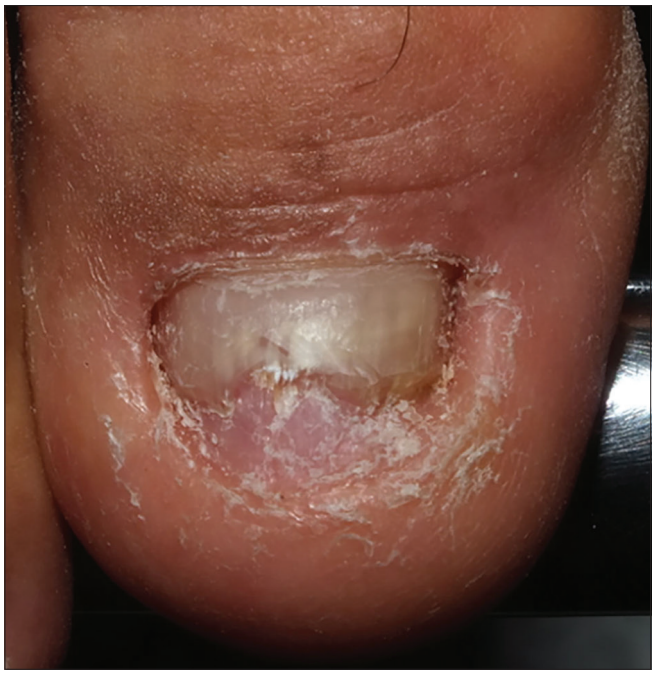

Figure 1e: 30% Dimethyl sulfoxide cream at baseline. Representative photographs of clinical improvement in onychomycosis treated with amphotericin B cream and vehicle cream

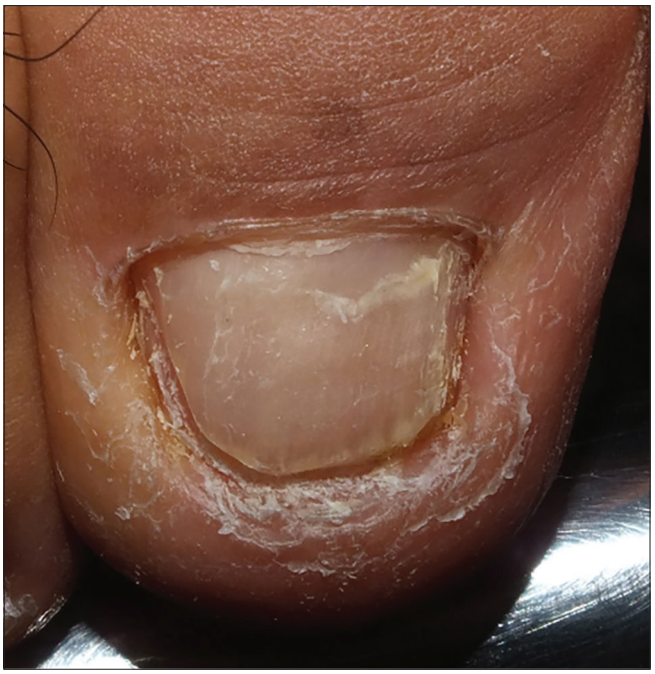

Figure 1f: 30% Dimethyl sulfoxide cream at 3 months. Representative photographs of clinical improvement in onychomycosis treated with amphotericin B cream and vehicle cream

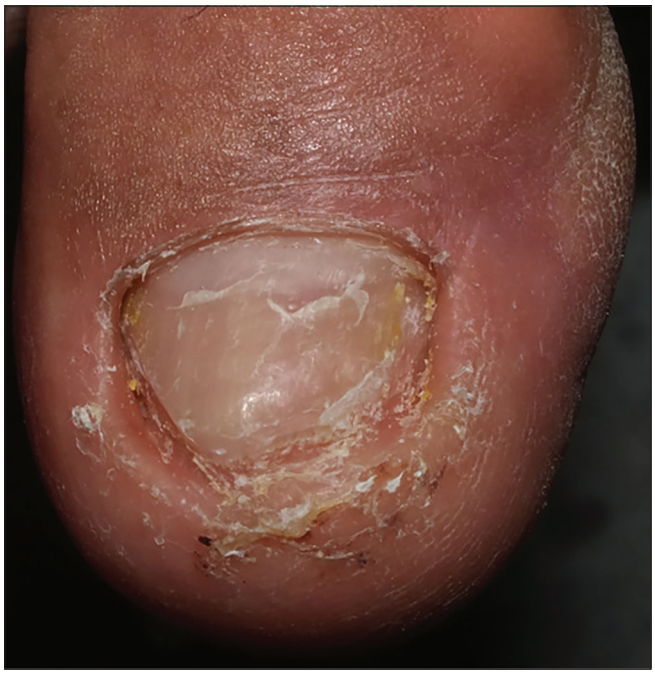

Figure 1g: 30% Dimethyl sulfoxide cream at 6 months. Representative photographs of clinical improvement in onychomycosis treated with amphotericin B cream and vehicle cream

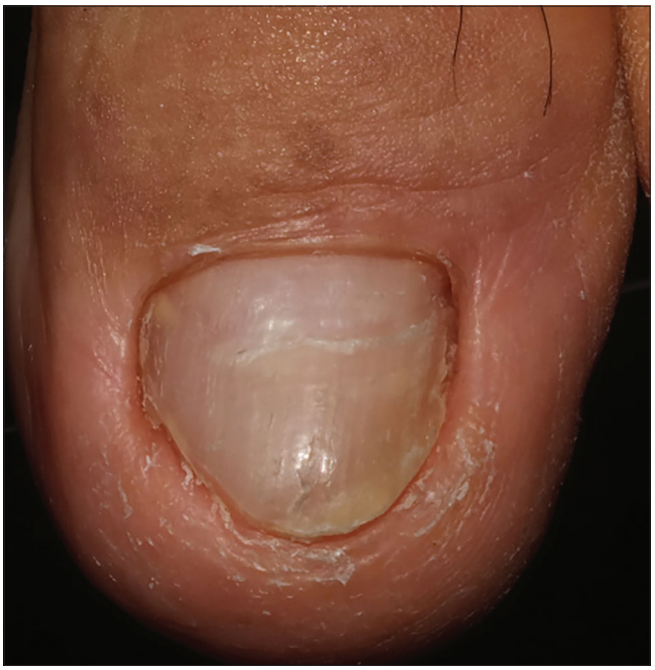

Figure 1h: 30% Dimethyl sulfoxide cream at 12 months. Representative photographs of clinical improvement in onychomycosis treated with amphotericin B cream and vehicle cream

treatment of nondermatophyte mold onychomycosis with 5% amorolfine nail lacquer and neodymium-doped yttrium aluminum garnet (Nd: YAG) 1064-nm laser resulted in only a marginally higher mycological cure rate of 65% as compared to 60% in those using 5% amorolfine nail lacquer alone.[27]

Amphotericin B has excellent in vitro activity against nondermatophyte molds.[5,13-15] In a study from Switzerland mycological cure was achieved with 0.2 % topical amphotericin B in 50% dimethyl sulfoxide in 7 (87.5%) of 8 treatment-resistant nondermatophyte mold onychomycosis patients at 12 months.[17]This compares well with the mycological cure rate of 80% in our study, although we used 0.3% amphotericin B in 30% dimethyl sulfoxide cream.[27]

The mycological and clinical cure rates of 44% and 22%, respectively, with the 30% dimethyl sulfoxide vehicle cream was an unexpected finding in our study. Dimethyl sulfoxide

has both keratolytic [28,29] and antifungal properties and has been shown to inhibit the growth of dermatophytes and yeasts in vitro.[21,30,31]

Limitations

Limitations of the study include the small sample size and the non-availability of PCR fungal identification which provides accurate identification of fungal species was not used in this study. As all cases were the distal lateral subungual type, treatment response according to clinical type of onychomycosis could not be identified. Although all four cases of fusarium spp onychomycosis responded to amphotericin B in our study, it is difficult to draw any firm conclusions owing to the small numbers.

Validation through a larger sample size is needed to conclusively demonstrate the effects of not only amphotericin B, but also the 30% dimethyl sulfoxide vehicle cream for nondermatophyte mold onychomycosis treatment.

Conclusion

Amphotericin B in 30% dimethyl sulfoxide was effective and safe in the treatment of nondermatophyte mold onychomycosis. However, the vehicle cream containing 30% dimethyl sulfoxide also showed some effectiveness in nondermatophyte mold onychomycosis.

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Declaration of patient consent

Institutional Review Board (IRB)/Institutional Ethics Committee (IEC) permission obtained for the study.

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Conflicts of interest

There are no conflicts of interest.

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