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The use of topical therapies to treat onychomycosis

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Onychomycosis is a fungal infection of the nail unit, which has become increasingly prevalent. Factors that may be attributed to the rise in the prevalence of onychomycosis include an increase in the use of immunosuppressive therapies; aging of the population; tight-fitting footwear; and the use of communal areas (eg, public baths, gymnasiums, health spas, hotel rooms, and so forth). Onychomycosis has been reported to be more prevalent in men than women, among the elderly, diabetics, and other immunocompromised individuals [1–3].

Therapeutic options for the treatment of onychomycosis include no therapy, palliative care, mechanical or chemical debridement, topical and systemic antifungal agents, or a combination of two or more of these modalities. Factors that influence the choice of therapy include the presentation and severity of the disease, the current medications the patient is taking, previous therapies for onychomycosis and their response, physician and patient preference, and the cost of therapy.

The clinical presentations of onychomycosis include distal-lateral subungual onychomycosis, proximal subungual onychomycosis, white superficial onychomycosis, endonyx onychomycosis, and total dystrophic onychomycosis. White superficial onychomycosis should respond best to topical therapy because of the superficial nature of this infection. In many instances, it may be possible to mechanically remove the diseased portion of nail using a curette or a similar device; in fact, the day-to-day activities of some patients may produce enough trauma to the nail to dislodge or remove the diseased portion of the superficial nail from the normal-appearing nail.

To determine the extent of the literature relating to the use of topical agents for the management of onychomycosis, a Medline search was conducted from the years 1966 to June 2002. The key words that were used included "topical" and "onychomycosis." Studies were excluded [4–12] for reasons including retrospective nature; preliminary data; non-English language format; unable to extract relevant data; only special populations (eg, transplant patients, diabetic patients, and so forth) enrolled; clinical presentations other than distal lateral subungual onychomycosis evaluated; and trials where only fingernail onychomycosis was considered for treatment. This article is confined to the treatment of distal and lateral subungual onychomycosis.

Efficacy parameters

Twenty-six studies were included in the evaluation of topical therapies [13–38]. Most studies did not define the efficacy parameters used to determine whether a treatment was successful. When efficacy parameters were defined, they were often variable. For instance, mycologic cure was defined as "negative culture and KOH" [13,15,19,24,27,34], "negative culture" only [31], or "negative culture and a negative or missing microscopy result" [22]. Clinical

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response was defined as less than or equal to 10% nail involvement and negative mycology [13], cure or markedly improved [22], percent of involvement [28,29], or 100% remission or 90% to 99% improvement [34]. Complete cure was defined as clear nail and negative mycology [13,15,19,27,34], clinical cure and negative culture [31,32], clinical cure and negative microscopy [38], neither clinical nor microscopic evidence of reinfection [35], or complete clinical recovery and negative microscopy [23].

Ciclopirox and amorolfine nail lacquers

The active component in the nail lacquer polymer film is maintained on the nail surface, from which it evenly diffuses through the nail plate keratin thereby reaching the nail bed [39]. After the evaporation of the solvent, the concentration of the active ingredient, ciclopirox or amorolfine, increases to 34.8% and 25%, respectively [39,40]; this enhances transungual diffusion [39].

Ciclopirox nail lacquer

Ciclopirox solution 8% is the only approved nail lacquer in the United States for the treatment of onychomycosis. This hydroxypyridone derivative has been marketed worldwide for approximately 25 years and is approved in more than 40 countries worldwide [41]. In December 1999, the nail lacquer was approved in the United States for the treatment of mild to moderate onychomycosis of the fingernails and toenails without lunula involvement, caused by *Trichophyton rubrum* [13,41].

Mode of action

Ciclopirox has a diverse mode of action that targets different metabolic processes in the microbial cell [42]. The main mode of action is its high affinity for trivalent cations, such as Fe^{3+} and Al^{3+} [43]. The inhibition of these essential cofactors affects mitochondrial electron transport processes in the course of energy production, thereby impairing microbial metabolism [42].

Ciclopirox also strongly reduces the activity of catalase and peroxidase, which are responsible for the intracellular degradation of toxic peroxides. In addition, nutrient uptake into the internal pool of growing cells may be adversely affected; this can result in intracellular depletion of essential amino acids and nucleotides, which reduces the synthesis of proteins or nucleic acids [42].

Activity of ciclopirox

Ciclopirox is a broad-spectrum antifungal agent that exhibits fungicidal activity in vitro against dermatophytes, *Candida* species, and some nondermatophyte molds. In addition, ciclopirox exhibits antibacterial activity against a number of gram-positive and gram-negative aerobic and anaerobic bacteria [42]. Ciclopirox exhibits anti-inflammatory activity by preventing the formation of 5-lipoxygenase inflammatory mediators, such as 5-hydroxyeicosatetraenoic acid and leukotriene B_4; cyclooxygenase inflammatory mediator release (prostaglandin E_2); and the cyclooxygenase-mediated synthesis of prostaglandins [42].

Pharmacokinetics

In five patients with dermatophyte onychomycosis, a once daily application of ciclopirox nail lacquer for 6 months resulted in serum levels of the drug ranging between 12 and 80 ng/mL and a mean absorption of less than 5% of the applied dose; 1 month after the end of therapy serum and urine levels were below the level of detection [13]. Ciclopirox may be detectable in the nail for up to 2 weeks after discontinuing the application of the nail lacquer [42].

In two vehicle-controlled trials, patients applied ciclopirox topical solution 8% to all toenails and affected fingernails. Twenty-four of 66 randomly chosen patients had detectable serum ciclopirox concentrations in the range of 10 to 24.6 ng/mL at some point during treatment [13]. In an in vitro investigation, radiolabeled ciclopirox applied once to avulsed onychomycotic toenails demonstrated penetration up to a depth of approximately 0.4 mm [13]. In addition, the more diseased the nail (eg, rougher and more fissured nail surfaces) the greater the degree of penetration [44].

Efficacy

Table 1 is a summary of the randomized controlled trials (RCTs) where ciclopirox nail lacquer 8% was used to treat onychomycosis caused by dermatophytes, nondermatophytes, and yeasts. In this literature search, two RCTs [13], one open study [36], and two case reports [20] were found.

In the two randomized, double-blind, vehicle-controlled studies, 30 (29%) of 105 and 41 (36%) of 115 patients who applied ciclopirox for 48 weeks were mycologically cured [13]. In an open multicenter study, 60 patients with onychomycosis caused by nondermatophyte molds (*Scopulariopsis brevicaulis*, *Aspergillus niger*, *Aspergillus fumigatus*, and *Hendersonula toruloidea*) were treated with ciclopirox at least once weekly for up to 6 months

Table 1
Summary of RCTs where ciclopirox nail lacquer 8% solution has been used to treat onychomycosis

Study location	Study type	Nail matrix involvement	Treatment	MC[a] (%)	CR[b] (%)	Complete cure[c] (%)	Species identified
United States	Double-blind, randomized, vehicle-controlled, parallel-group, multicenter [13,46]	No	Ciclopirox applied once daily for 48 weeks	30/105 (29)	7/107 (6.5)	6/110 (5.5)	*T rubrum*, *T mentagrophytes*
			Vehicle applied once daily for 48 weeks	12/106 (11)	1/108 (0.9)	1/109 (0.9)	
United States	Double-blind, randomized, vehicle-controlled, parallel-group, multicenter [13,46]	No	Ciclopirox applied once daily for 48 weeks	41/115 (36)	14/116 (12)	10/118 (8.5)	*T rubrum*, *T mentagrophytes*
			Vehicle applied once daily for 48 weeks	10/114 (9)	1/115 (0.9)	0/117 (0)	

[a] MC (mycologic cure): negative KOH and negative culture.
[b] CR (clinical response): ≤10% nail involvement and negative mycology (culture and KOH).
[c] Complete cure: clear nail and negative mycology (culture and KOH).

[36]. The mycologic cure rates reported were 85% (KOH preparation) and 90% (culture); however, the combined mycology result was not stated [36]. In a case report, a 75-year-old man applied ciclopirox nail lacquer 8% daily to the toenails for 6 months; this led to the progressive disappearance of symptoms associated with moderate to severe onychomycosis [20].

Tosti et al [7] treated patients with toenail onychomycosis caused by nondermatophyte molds. The clinical presentations included proximal subungual onychomycosis, white superficial onychomycosis, and distal subungual onychomycosis. Twenty-one patients had distal subungual onychomycosis caused by *S brevicaulis*, *Fusarium* species, and *Acremonium* species. The authors concluded that topical therapy was effective in the treatment of onychomycosis caused by some nondermatophyte molds [7].

Combination therapy with ciclopirox nail lacquer

A multinational, multicenter, randomized, and evaluator-blinded study is currently evaluating the combination of ciclopirox nail lacquer with terbinafine for the treatment of toenail onychomycosis with involvement of 60% or greater nail plate or matrix disease [45]. Patients receive one of three treatments: (1) terbinafine, 250 mg/d for 12 weeks with 48-week once daily application of ciclopirox nail lacquer; (2) terbinafine, 250 mg/d for 12 weeks; and (3) terbinafine, 250 mg/d for 8 weeks using an intermittent regimen with ciclopirox nail lacquer once daily for 48 weeks [45].

Safety

The most common adverse events are the appearance of a rash (eg, periungual erythema and erythema of the proximal nail fold), with some patients reporting a burning or tingling sensation at the application site [13]. Nail disorders were infrequently reported for both the ciclopirox and vehicle group, and consisted of shape change, irritation, ingrown toenail, and discoloration [13]. The adverse reactions were generally mild and often resolved with continued application of ciclopirox nail lacquer [46].

Amorolfine nail lacquer

Amorolfine is a topical antifungal agent of the morpholine class. It has a broad-spectrum of activity against yeasts, dermatophytes, and molds responsible for superficial fungal infections. Amorolfine is available in many countries for the treatment of onychomycosis, but is not approved in the United States for this indication.

Mode of action

Amorolfine acts at two points in the ergosterol biosynthetic pathway, inhibiting Δ_{14}-reductase and $\Delta_{7\text{-}8}$-isomerase enzymes [47]. Inhibition of these enzymes leads to a lack of cell growth and cell death, and the accumulation of sterol molecules and ignosterol, a sterol containing a Δ_{14}-double bond [48]. The accumulation of ignosterol and other sterol molecules no longer fulfills the steric requirements of the fungal membrane [48]. Also, ignosterol accu-

mulation in *Candida albicans* indicates inhibition of Δ_{14}-reductase [48,49].

Amorolfine activity

Amorolfine demonstrates fungicidal activity toward dermatophytes, dimorphic fungi, *C albicans*, *Cryptococcus neoformans*, and dematiaceous fungi; activity is both time and concentration dependent [47,49]. This morpholine derivative has also demonstrated fungistatic activity toward a number of fungal species [47,49].

Pharmacokinetics

An in-vitro penetration study examined the penetration of amorolfine (1%, 2%, and 5%) through porcine hoof horn material [50]. The highest accumulation of the drug was seen with the 5% amorolfine lacquer [50]. The penetration profile of the 5% amorolfine lacquer was examined over a 7-day period, where the concentration of amorolfine 5% in the nails increased linearly with a slight curve-shaped line, indicating saturation kinetics [50]. The kinetics of amorolfine in human nails follows an exponential law and the concentration of amorolfine in the upper layer of the nail plate is approximately 100 times higher than in the lowest layer [51]. The total amount of amorolfine in the nail depends on the thickness and consistency of the nail plate [51].

There are data in the literature on two galenic forms of amorolfine, one containing methylene chloride and the other ethanol. Franz [52] examined these two formulations to determine their affect on 5% amorolfine absorption. The rate of amorolfine absorption through a human thumbnail, following a single application, peaked between 5 and 25 hours and declined slowly thereafter in both the methylene chloride and ethanol lacquer. Rates of permeation through the nail ranged between 20 and 100 ng/cm^2/h [52]. In addition, Franz [52] found that amorolfine absorption was somewhat greater from the methylene chloride lacquer than the ethanol lacquer; however, Mensing et al [53] found no statistically significant difference between the two lacquer formulations.

Efficacy

Table 2 is a summary of the RCTs where amorolfine nail lacquer 5% has been used to treat onychomycosis caused by dermatophytes, nondermatophytes, and yeasts. In this literature search three RCTs [26,31,32] were found.

In a comparison study, Lauharanta [26] found 5% nail lacquer was significantly more effective than 2% nail lacquer when applied once weekly for up to 6 months for the treatment of mild to moderate onychomycosis. Two open, randomized studies com-

Table 2
Summary of RCTs where amorolfine nail lacquer 5% solution has been used to treat onychomycosis

Study type	Matrix involvement	Treatment	Follow-up	MC[d] (%)	CR[d] (%)	Complete cure+ (%)	Species identified
Open, randomized, parallel, comparative [31]	No	Amorolfine 5% once weekly for 6 mo	3 mo after treatment end	114/160 (71.2)[a]	120/160 (75)[b]	73/160 (45.6)[c]	*T rubrum*, *T mentagrophytes*, yeasts, others
		Amorolfine 5% twice weekly for 6 mo		125/166 (75.3)[a]	128/166 (77.1)[b]	86/166 (51.8)[c]	
Open, randomized, multicenter, comparative [32]	No	Amorolfine 5% once weekly for 6 mo or more	3 mo after treatment end	89/126 (70.6)		58/126 (46)[c]	*T rubrum*, *T mentagrophytes*, yeasts, others
		Amorolfine 5% twice weekly for 6 mo or more		108/142 (76.1)		77/142 (54.2)[c]	
Double-blind, randomized, parallel-design, multicenter [26]	No	Amorolfine 5% once weekly for up to 6 mo	3 mo after treatment end	31/51 (60)		(38)	*T rubrum*, *T mentagrophytes*, yeasts, others

[a] MC (mycologic cure): negative culture.
[b] CR (clinical response): cure or ≤10% of nail still affected.
[c] Complete cure: clinical cure and negative mycologic culture.
[d] Efficacy parameter not defined unless otherwise stated.

pared the efficacy and safety of once-weekly versus twice-weekly application of amorolfine [31,32]. Both studies found that cure rates were slightly higher in the twice-weekly groups; however, there was no statistically significant difference between the dosage regimens [31,32].

Combination therapy with amorolfine nail lacquer

In an open, multicenter study 147 patients were randomized to receive amorolfine 5% applied once weekly for 15 months in combination with terbinafine (250 mg/d) administered for 6 weeks (AT6) or 12 weeks (AT12), or terbinafine, 250 mg/d for 12 weeks (T12) [15]. At the end of the 18-month study, greater than 70% of the AT6 patients, approximately 90% of the AT12 patients, and greater than 60% of the T12 patients were mycologically cured (both negative microscopy and culture). The corresponding values for global cure (combined clinical-mycologic response) were 44% (N = 50), 72.3% (N = 47), and 37.5% (N = 48), respectively. The authors concluded that the combination of amorolfine and terbinafine might be an effective treatment for severe onychomycosis with nail matrix involvement [15].

In a similar study, Lecha et al [27] compared the efficacy of combined topical amorolfine and itraconazole with itraconazole alone in the treatment of severe toenail onychomycosis, defined as greater than or equal to 80% involvement of the surface or the matrix region of at least one toenail. Patients were treated with amorolfine 5% nail lacquer once weekly for 6 months in combination with itraconazole (200 mg/d) for 6 weeks (AI-6) or 12 weeks (AI-12), or itraconazole, 200 mg/d for 12 weeks (I-12) [27]. At week 24, statistically more patients in the combined treatment group ($\geq$ 90%) were mycologically cured (negative microscopy and culture) compared with those treated with itraconazole (< 69%) alone ($P < .001$). Clinical cure (reduction of $\geq$ 95% in the original diseased nail surface area) was observed at week 24 in 88.1%, 100%, and 90.3% in the AI-6, AI-12, and I-12 groups, respectively. The corresponding values for global cure (combined mycologic-clinical outcome) were 83.7%, 93.9%, and 68.8%, respectively [27].

Safety

Amorolfine nail lacquer seems to be a safe treatment of onychomycosis. Adverse events reported by patients included burning, itching, redness, and local pain; these symptoms were tolerable and confined to the application site [31,32]. Few complained of local irritation [31,32]. There have been no reports of nonlocal adverse events experienced by the patient.

Other topical therapies

Efficacy

Several topical antifungal agents have been used to treat onychomycosis including tioconazole [35,38], miconazole [16,22,33,35], fungoid tincture [28,29], bifonazole urea [17,24], tea tree oil [18,34], topical ketoconazole [25], ciclopirox olamine cream [30,37], and vitamin E [21]. Most of these studies evaluated the effectiveness of topical agents in the treatment of onychomycosis caused by dermatophytes.

Table 3 is a summary of the RCTs where topical agents other than ciclopirox and amorolfine nail lacquers have been used to treat onychomycosis caused by dermatophytes, nondermatophytes, and yeasts. In this literature search, five RCTs [18,22,29,34,35], nine open studies [16,17,24,25,28,30,33,37,38], and one case report [21] were found.

In the RCTs, few studies mentioned the causative organism. Tea tree oil 5% combined with 2% butenafine was significantly more effective than tea tree oil alone ($P < .0001$) [34]. Miconazole cream was significantly less effective compared with oral itraconazole [22].

In an open study, Hay et al [38] evaluated the effectiveness of tioconazole 28% nail solution in the treatment of 27 patients with onychomycosis. Six patients, five of whom had fingernail infections, were clinically and mycologically free from infection 2 to 7 months after treatment [38]. Eleven patients showed marked improvement [38].

In an open, multicenter trial, 57% of the onychomycosis patients treated with a combination of 1% ciclopirox solution and cream for a mean duration of 12.7 $\pm$ 5.6 weeks were free from signs of infection [30]. In an open study, ciclopirox olamine 1% cream was applied two to three times daily for 3 to 24 months in 42 patients with onychomycosis [37]. Fourteen percent of the patients were cured and 36% improved with treatment [37].

Avulsion of the onychomycotic nail before the application of topical agents may be beneficial. The topical treatment of onychomycosis with 1% bifonazole and 40% urea paste produced mycologic cure (negative direct microscopy and culture) rate of 62.5% at week 12 [24]. A similar study, evaluating the effectiveness of 1% bifonazole and 40% urea paste, demonstrated that at month 4, 45 (90%) of 50 patients were culture negative [17].

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