

Update on terbinafine with a focus on dermatophytoses

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Abstract: Since terbinafine was introduced on the world market 17 years ago, it has become the leading antifungal for the treatment of superficial fungal infections, aided by unique pharmacologic and microbiologic profiles. This article reviews mode of action, antimycotic spectrum and disposition profile of terbinafine. It examines the data, accumulated over 15 years, on the comparative efficacy of terbinafine (vs griseofulvin, itraconazole, fluconazole) in the management of the infections for which it is primarily indicated (eg, dermatophytoses) and provides a brief discussion on its use for the treatment of non-dermatophyte infections. Finally, the available data on the newest topical and systemic formulations are introduced.

Keywords: tinea, *Trichophyton*, *Microsporum*, allylamine, antifungal

Introduction

In 2008, oral terbinafine reached the 12-year mark in the United States (US) and 17 years on the world market. Since its launch, terbinafine has garnered the top slot among topical antifungals and the oral formulation is estimated to have captured nearly 80% of the greater than US\$1.5 billion worldwide onychomycosis market (although it makes up only a minority of prescriptions written for children).^{1,2} Terbinafine remains the only commercially available orally available allylamine and shares the topical allylamine/benzylamine market with naftifine, butenafine and amorolfine. In recent years several new formulations have been added to the portfolio of this antimycotic including a pediatric oral granule approved by the US Food and Drug Administration in September of 2007 and a single-dose, film-forming topical solution that is now available over the counter in a number non-US markets.

This article will review the accumulated data on the mycology and pharmacology of terbinafine including its mode of action, antimycotic spectrum, disposition profile and therapeutic efficacy. The primary focus will surround dermatophytoses with a brief discussion on the role, to date, of terbinafine in non-dermatophyte infections.

Clinical mycology

Discovered in 1983, terbinafine is a member of the allylamine class of antifungals. It differs from its parent compound, naftifine, by the presence of a tert-butyl acetylene substitution of the phenyl ring on the side chain of the molecule. This substitution confers an increase in oral efficacy and an additional 10 to 100 times the in vitro activity of naftifine.^{3,4}

Terbinafine inhibits fungal growth by disrupting sterol biosynthesis. It abrogates the formation of ergosterol by inhibiting squalene epoxidase, the catalytic enzyme responsible for converting squalene to 2,3-oxidosqualene (an ergosterol precursor). The resultant deficiency in ergosterol compromises cell wall integrity and contributes to impaired growth and/or death of the pathogen.⁵⁻⁷ Notably, the biosynthesis of cholesterol in higher order eukaryotes similarly relies on the activity of squalene

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epoxidase; however, terbinafine demonstrates a markedly lower binding affinity for the mammalian enzyme. In vitro, the minimum concentration of terbinafine required to inhibit 95% of squalene epoxidase activity (IC_{95}) is two to three orders of magnitude greater for the mammalian enzyme (300 μ M) than for enzymes isolated from pathogenic yeast (0.6–2.1 μ M).⁷

While the majority of clinical terbinafine use is observed with infections caused by dermatophytes, the susceptibility of numerous organisms including pathogenic yeast, dematiaceae, thermally dimorphic fungi and hyaline hyphomycetes has been evaluated.^{8–16} Although the nature of the assays employed precludes direct comparison of minimum inhibitory concentrations (MICs) between studies (ie, some were performed prior to standardization of a reference method by the Clinical and Laboratory Standards Institute (CLSI),¹⁷ some universal trends are repeated throughout. Namely, terbinafine demonstrates the greatest activity against species within the *Trichophyton*, *Microsporum*, and *Epidermophyton* genera followed by the dematiaceae, the filamentous fungi and a few selected pathogenic yeast.

The terbinafine MICs observed against the dermatophytes are typically several orders of magnitude lower than those reported for other fungi.^{18–23} This heightened susceptibility is reflected by an MIC that is an order of magnitude lower than IC_{95} for sterol biosynthesis.⁶ Given that dermatophyte growth can be fully inhibited despite only partial inhibition of sterol synthesis, the activity of terbinafine is likely accounted for by other processes including the intracellular accumulation of squalene.³ In contrast, the MIC to IC_{95} ratio for several species of fermentative yeast equals or exceeds one.⁶ Compared with dermatophytes, these organisms have adapted to survive under anaerobic growth conditions which are characterized by low ergosterol and high squalene concentrations.⁶ Reasonably, it is expected that such organisms would be less susceptible to the effects of a squalene epoxidase inhibitor.

The MICs reported for terbinafine against various dermatophytes are typically comparable to or lower than those of other antifungals active against these organisms, namely the triazoles, imidazoles and griseofulvin.²⁴ However, a direct comparison of MICs between therapeutic agents needs to be considered in the context of achievable concentrations at the site of infection. No significant differences in terbinafine susceptibilities exist between US and non-US isolates of selected *Trichophyton* and *Microsporum* species.²⁵ Further, the putative increase in resistance to azole antifungals observed with the “heartier” arthroconidia of the dermatophytes has

not been observed with terbinafine. Both arthroconidia and microconidia of selected *Trichophyton* species demonstrate the same susceptibility profile to terbinafine in vitro.²⁶

In addition to diminished susceptibility, non-dermatophyte species of fungi demonstrate resistance mechanisms not observed in the dermatophytes. Under the selective pressure of terbinafine exposure, an increase in the expression of energy-dependent efflux transporters can be observed in yeast;²⁷ however, the expression level of orthologous transporters remains unchanged in dermatophytes.²⁸ Similarly, filamentous fungi can upregulate the expression of an enzyme that catalyzes the breakdown of terbinafine²⁹ but this has not been reported for dermatophytes.

Overall, an extremely low rate of spontaneous mutation conferring resistance of dermatophytes to terbinafine exists in vitro.³⁰ Nonetheless, reduced susceptibility to terbinafine has been observed in clinical dermatophyte isolates. These appear to arise from clones harboring one of two described sequence variations in the squalene epoxidase gene.^{31,32} As the reported mutations do not appear to impact fungal growth in the absence of terbinafine,³³ they likely signal changes to the terbinafine binding domain and ultimately binding affinity of the drug for the protein.³⁴

While spontaneous resistance is rare, increasing reports describe cross-resistance developing between other antifungals and terbinafine. Under the selective pressure of echinocandin exposure in vitro, the upregulation of efflux transporters in yeast also reduced susceptibility to terbinafine.³⁵ Similarly, azole “pre-exposure” in yeast can diminish susceptibility of the organisms to terbinafine.^{36–38} Notably, the aforementioned mechanisms of cross-resistance have not been reported for dermatophytes, in vitro or in vivo, after protracted imidazole treatment.^{36–38}

Of potentially significant clinical relevance is the activity of terbinafine when used in combination with other antifungals for the management of invasive mycoses. Against *Aspergillus fumigatus*, indifference was primarily observed when terbinafine was combined with amphotericin B. Similarly, terbinafine did not improve the activity of fluconazole or itraconazole against *A. fumigatus*; however, the triazoles demonstrated synergism when added to terbinafine.³⁹ Against fluconazole-resistant yeast, synergy with fluconazole and itraconazole was observed in a fraction of isolates, *Candida glabrata* > *Candida tropicalis*, > *Candida kreusii*.^{40,41} In these pathogenic yeast antagonism has also been observed among these antifungals.⁴¹ Against ocular isolates of *Fusarium*, the combination of amphotericin B and terbinafine was synergistic, while the combination of terbinafine and

triazoles demonstrated indifference.⁴² The ultimate utility of terbinafine in the management of invasive infections will be determined as more experience is obtained utilizing this agent as adjunct therapy.

Clinical pharmacology (Tables 1 and 2)

Terbinafine is efficiently absorbed following oral administration (bioavailability approx. 70%) and this does not appear to be affected by feeding status.^{51,52} Over the range of clinically relevant doses (125–750 mg) terbinafine demonstrates a linear absorption profile with total body exposure increasing in direct proportion to dose.⁵³ The rate of absorption does not appear to differ substantially between children and adults. However, the extent of absorption as reflected by maximum plasma concentrations is markedly lower in children when doses are normalized per kilogram of body weight.⁴³

Following topical administration to normal skin, cream- and gel-based terbinafine formulations attain concentrations ranging from 746 to 949 ng/cm².^{48,54} Maximum stratum corneum concentrations increase by 15% with 7 days of application; however, the area under the plasma concentration vs time curve (AUC) can increase by as much as 40% over 1 week.⁵⁴ Notably, concentrations obtained in the horny layer of patients with an active infection can be up to an order of magnitude lower than that observed in healthy individuals.⁵⁵ While topical preparations are well absorbed into the stratum corneum, the resultant systemic exposure is several orders of magnitude lower than observed after oral terbinafine administration (Tables 1 and 2).

Terbinafine is extensively distributed with estimates of apparent distribution volume approaching 20 L/kg.^{53,56} This relatively large volume of distribution results from the drugs

high degree of lipophilicity, extensive protein binding profile and ability to concentrate in adipose and keratin rich tissue.^{56,57} At steady-state, concentrations observed in sebum, stratum corneum and hair exceed those observed in the plasma by as much as an order of magnitude. Although lower in the stratum corneum of hyperkeratotic tissue, terbinafine concentrations remain elevated following the discontinuation of oral therapy and persist in excess of 1 month after stopping treatment.⁵⁸

At least seven cytochromes P450 (CYP) appear to be responsible for metabolizing terbinafine into more than 15 metabolites.⁵⁹ In adults, the N-demethyl and carboxybutyl metabolites constitute the largest fraction of the metabolites observed. Maximum circulating concentrations and total body exposure are comparable or in excess of those observed with the parent compound. Notably, the circulating half-life for the carboxy metabolites were twice as long as that of terbinafine.⁴⁶ Although the metabolites lack an appreciable antifungal activity, they may contribute to the drug interactions and/or side effects observed following administration.^{51,60}

Given the polyfunctional nature of terbinafine as a substrate for the CYP450, the magnitude of potential drug interactions would be predicted to be low as compared with other drugs.^{61–63} However, this is not the case for interactions mediated by CYP2D6. Terbinafine exhibits potent inhibition of this enzyme in vitro (apparent inhibitor rate constant (k_i) approx. 30 nM) and correspondingly marked reduction in the metabolism of the CYP2D6 substrate dextromethorphan in vivo.^{60,64} Importantly, the activity of CYP2D6 may not return to normal for months after the completion of a prolonged course of therapy.⁶⁴ Clinically, terbinafine is demonstrated to interact with concurrently administered CYP2D6 substrates including amitriptyline, nortriptyline, desipramine, and

Table 1 Pharmacokinetic parameter estimates of terbinafine following oral administration

Parameter ^a	Adults 125 mg single-dose (n = 26) ^{43,44}	Adults 250 mg single-dose (n = 29) ^{45,46}	Adults 125 mg steady-state (n = 10) ⁴³	Adults 250 mg steady-state (n = 22) ^{46,47}	Children 125 mg single-dose (n = 28) ^{43,44}	Children 125 mg steady-state (n = 16) ⁴³
T _{max} (h)	1.3–1.5	1.4–1.5	1.6	1.2	1.7–2.1	1.8
C _{max} (ng/mL)	506–565	1340–1656	646	1700 ^b	706–909	1059
AUC (h*ng/mL)	1624–2135	4740–6762	3720	10481	2967–4104	5851
Cl/F (L/h/kg)	1.2		0.55	0.4	1.9	1.7
V _{ss} /F (L/kg)	19.2				19.5	
τ _{1/2α} (h)	0.7	0.35			1.2	
τ _{1/2β} (h)	26.7	12.6–14.2			14.7	
τ _{1/2γ} (h)				396	156	

Notes: ^aValues represent the mean reported values from the referenced studies (when more than one study is referenced, values represent the range of reported mean values). ^bCorresponding peak tissue concentrations: hair, 2.4 μg/g; stratum corneum, 14.4 μg/g; sebum, 56.1 μg/g.

Abbreviations: T_{max}, time at maximum plasma concentration; C_{max}, maximum plasma concentration; AUC, area under the plasma concentration vs time curve; Cl/F, apparent oral clearance; V_{ss}/F, steady-state volume of distribution; τ_{1/2α}, alpha-phase half-life; τ_{1/2β}, beta-phase half-life, τ_{1/2γ}, gamma-phase or terminal half-life.

Table 2 Local and systemic estimates of exposure following topical terbinafine application

Parameter ^a	1% gel × 7 days healthy skin ^{48,49}	1% cream 7 days ^{48,50,54}	1% FFS I application ⁵⁰
Stratum corneum C _{max} (μg/cm ²)	0.91	0.94–2	5
Stratum corneum AUC (h*μg/cm ²)	12.7	11.7–13.5	104.2
Tissue t _{1/2} (h)	1.2	68	162
Plasma C _{max} (ng/mL)	3.82		
Plasma AUC (h*ng/mL)	63		

Notes: ^aValues represent the mean reported values from the referenced studies (when more than one study is referenced, values represent the range of reported mean values).
Abbreviations: C_{max}, maximum observed concentration, AUC, area under the concentration vs time curve; t_{1/2}, half-life.

venlafaxine.^{65–68} Other drugs harboring the potential to interact with terbinafine include perphenazine, metoprolol, encainide and propafenone.⁶⁹

For drugs that are not substrates of CYP2D6 (eg, anti-coagulants, corticosteroids, oral contraceptives, tolbutamide, cyclosporine, midazolam, digoxin and terfenadine) terbinafine has only a modest or minimal affect on their metabolism.^{70–74} However, as a substrate of the cytochromes P450, the pharmacokinetics of terbinafine are altered with the concurrent administration of several agents (eg, cimetidine, terfenadine, rifampin).^{70,75}

The clearance of terbinafine is triphasic with the terminal elimination half-life approximating 100 hours after a single dose and 22 days with durations of therapy spanning several months.^{44,76} Approximately 80% of terbinafine's metabolites are excreted by the kidney with the remaining fraction eliminated in the feces.⁴⁴ This protracted rate of elimination accounts for the magnitude of accumulation observed with terbinafine after repeated dosing and the persistence in plasma and tissues long after discontinuation of the drug.⁴⁷ While this confers a distinct advantage to the allylamine permitting shorter courses of therapy, it poses a unique disadvantage for patients experiencing drug-related adverse events.

Therapeutic use

Terbinafine is indicated for use in the management of cutaneous dermatophytoses (eg, tinea corporis, tinea cruris and tinea pedis), onychomycosis and most recently tinea capitis. In addition, terbinafine use has been explored in a number of superficial and systemic mycoses involving pathogens other than the dermatophytes. The results of open-label and randomized trials exploring the utility of terbinafine in various infections is detailed in the following sections.

Cutaneous dermatophytoses

Dermatophyte infections of the glabrous skin, groin and feet can be caused by any of a number of dermatophyte species.⁷⁷

While these infections typically respond to topical antifungals, oral therapy is often indicated when the lesions are widespread or chronic in nature.⁷⁸

Terbinafine applied topically as a 1% cream, gel or solution demonstrates utility in the management of both tinea corporis and tinea cruris.⁷⁹ The application of terbinafine once-daily for 7 to 14 days resulted in mycological cure rates ranging from 84% to 94%, clinical cure rates ranging from 75% to 84% and overall efficacy rates ranging from 65% to 83%.^{80–86} The observed treatment response with topical terbinafine is significantly greater than reported for placebo wherein clinical, mycological and complete cure rates range from 8% to 22%.^{81,83} Topically applied terbinafine also demonstrated statistically greater mycological response rates than a 2-week course of 2% ketoconazole cream,⁸⁰ whereas clinical response rates were comparable to a 0.6% gel containing the garlic-derived, sulfuric compound ajoene.⁸⁴

Following oral administration for the treatment of tinea corporis and tinea cruris, clinical and mycological cure rates observed with terbinafine have ranged from 71% to 100% and 78% to 100%, respectively.^{78,87–89} No significant differences in mycological or clinical cure rates were observed between terbinafine and griseofulvin in these studies;^{87–89} however, higher relapse rates were observed with griseofulvin.^{88,89} Tinea imbricata, a variant of tinea corporis found predominantly in tropical countries, manifests as concentric rings of papular plaques that are chronic in nature and relatively recalcitrant to antifungal therapy. In a single randomized, controlled trial 4 weeks of treatment with terbinafine demonstrated higher overall efficacy rates (100%) and lower relapse rates (16%) as compared with itraconazole (89% efficacy, 75% relapse).⁹⁰

Tinea pedis is a dermatophyte infection of the foot that generally takes one of three forms: 1) interdigital infections characterized by cracking and fissuring of the skin in the webbing between the toes, 2) acute vesicular infections which present with erythema, bullous eruptions and bacterial

super-infections and 3) a chronic form of infection with scaling that covers the entire foot typically referred to as “dry” or “moccasin” type tinea pedis.⁹¹ The nature and extent of infection often determines whether oral therapy is required or whether symptomatic relief can be obtained with topical therapy.⁹²

Although topical terbinafine formulations in excess of 1% have been investigated, superficial treatment of tinea pedis typically relies on 5 to 7 days of application with the 1% cream, gel or solution (as described above for infections of the skin and groin). Mycologic cure rates are comparable irrespective of formulation, ranging from 82% to 97% with overall efficacy rates of 64% to 86%. Response rates are significantly greater than observed with the vehicle alone wherein mycologic cure and overall efficacy range from 22% to 37% and 4% to 26%, respectively.^{83,93–96} Mycological cure rates, after 1 week of treatment, are also comparable to or greater than those observed after 4 weeks of treatment with topical azole preparations.^{97–99}

Despite the advantage of a strong efficacy profile with the application of terbinafine for one week, efforts to simplify topical administration, decrease treatment duration and improve compliance has led to the development of a polymeric film-forming solution (FFS) designed as a “one-time” dose. The acrylate/cellulose/triglyceride based formulation leaves a nearly invisible, highly-concentrated film on the skin after the carrier solvent (ethanol) has evaporated. This film remains on the site of infection nearly 6 times longer than other topical preparations and results in stratum corneum concentrations that are sustained above the MIC in excess of 2 weeks after application.^{50,100} FFS concentrations as high as 10% have been evaluated; however, mycological cure rates (80%–84%) and overall efficacy (61%–70%) 6 weeks after application did not appear to demonstrate dose-dependence.¹⁰⁰ Consequently, the currently marketed formulation contains 1% terbinafine. In a study examining slightly longer-term follow-up, mycological cure rates were observed in 72% of those treated. Notably, the duration of infection prior to treatment did not appear to influence the likelihood of mycological cure. When participants were re-evaluated at 3 months, 12.5% of those individuals considered mycologically cured at 6 weeks demonstrated positive cultures, comparable to the rates observed with other topical terbinafine formulations.¹⁰¹

For more refractory (eg, hyperkeratotic) infections of the foot, efficacy rates comparable to those described above can be observed with topical treatment; however, this may require protracted treatment durations (ie, several months).⁵⁵ In these

cases, oral therapy has emerged as a reliable alternative. Orally administered terbinafine can be highly effective in the management of tinea pedis with overall efficacy rates exceeding 90% depending on the nature of infection and the regimen used. The majority of investigations have examined the efficacy of orally administered terbinafine at daily doses of 250 mg (either divided or once daily). Efficacy rates after 6 weeks of treatment ranged from 59% to 75%, increasing to 65% to 88% 12 weeks after the end of therapy.^{102,103} This is compared with placebo and griseofulvin where efficacy rates were 0% and 27%, respectively at the end of treatment and 0% and 45%, respectively, 2 weeks post treatment.^{102,103} With shorter courses of oral treatment (250 mg daily × 2 weeks), mycological and clinical cure rates are markedly less impressive (23%–28% and 8%–43%, respectively). However, when followed out for 6 to 16 weeks, mycological cure rates (78%–86%) and clinical efficacy (71%–94%) improve dramatically suggesting utility with shorter treatment durations of terbinafine.^{104,105} Cure rates observed with terbinafine were comparable to those observed with itraconazole (100 mg/day); however, long-term follow-up suggested that terbinafine was slightly superior to 4 weeks of itraconazole treatment and significantly superior to 2 weeks of treatment with the triazole.^{104,105} Data from a single study each suggest that reducing (125 mg/day) or increasing (500 mg/day) the dose of terbinafine may not substantially alter cure rates compared traditional dosing with 250 mg/day.^{51,58}

Onychomycosis

Approximately one-half of all nail problems are accounted for by onychomycosis, a fungal infection wherein the nails become discolored, thickened and prone to peeling or splitting.¹⁰⁶ Dermatophytes are principally responsible for infections of the toenail, whereas over 50% of fingernail infections can be caused by non-dermatophyte species.^{107,108} Of the commercially available oral antifungals, griseofulvin, itraconazole and terbinafine are most commonly used for the management of onychomycosis. Efficacy rates and treatment durations vary although treatment with the latter agents typically requires shorter courses than does the former. Irrespective, the majority of studies described below document cure rates at 12 months or beyond (earlier for fingernails) to account for the protracted growth rate of nails and the extended time-frames over which drug remains in the affected nails.

Since its approval, scores of studies have evaluated numerous terbinafine dosing regimens for the treatment of onychomycosis. With the administration of daily 250 mg

doses, mycologic and clinical response rates observed in toenails ranged from 72% to 92% and 45% to 77%, respectively.^{109–113} Notably, there was little difference in both clinical and mycological response rates whether patients were treated for 12, 18 or 24 weeks.^{109,111–113} Infections of the fingernail demonstrated comparable response rates ranging from 71% to 100%.^{109,111,114} When non-dermatophyte pathogens are considered in subgroup analyses, response rates approximate 40% for infections with *Candida* and greater than 90% when treating *Scopulariopsis brevicaulis*.^{115–117} The combination of daily terbinafine doses (250 mg) with chemical or mechanical removal of the nail offers little to no additional increase in efficacy over terbinafine alone.^{118,119} Similarly, only limited increases in efficacy are observed when daily oral therapy is combined with adjunctive therapy including once-weekly topical amorolfine or once-daily topical ciclopirox.^{120–123} In each study topical therapy appeared to confer slight improvements in response; however, limited sample sizes restrict their significance and superiority over terbinafine alone could not be determined.

Intermittent terbinafine dosing has also been explored for the management of onychomycosis. When the standard regimen of 250 mg once daily was compared to intermittent dosing administered at 350 mg daily for 2 weeks followed by 2 weeks “off” for the management of subungual onychomycosis, both mycological (56%–58% vs 43%–50%) and complete cure (26%–30% vs 20%–24%) favored traditional dosing; however, only the latter was statistically significant.¹²⁴ When compared with 500 mg administered daily for 1 week (followed by 3 weeks off) for the treatment of distal subungual onychomycosis, traditional dosing again proved superior to intermittent dosing. Mycological cure of the target toenail (71% vs 59%); clinical cure of the target toenail (45% vs 29%); complete cure of the target toenail (40% vs 28%); and complete cure of all 10 toenails (25% vs 15%) were all statistically greater with standard dosing.¹²⁵ No significant differences in complete cure have been observed based on the number of pulses administered; however, a clear trend is noted with response rates increasing steadily from one to four pulses.¹²⁶ As noted with traditional dosing, higher cure rates were observed for fingernails treated with pulse-dosing as compared with toe nails. Mycological and clinical cure rates were 89% and 72% for dermatophytes, albeit lower (67%) for infections caused by yeast.¹²⁷ As expected based on the comparative data generated from traditional dosing trials, the combination of pulse therapy with ancillary topical therapy does not substantially improve outcome over treatment with terbinafine alone.^{126–128}

In two comparative trials, terbinafine (250 mg/day) was significantly superior to griseofulvin (500 mg/day). Mycological cure rates were significantly higher with terbinafine (84%–92% vs 45%–63%), time to mycological cure significantly shorter (73 vs 93 days) and clinical cure significantly higher (76% vs 39%) as compared with griseofulvin.^{129,130} However, the exclusion of non-dermatophyte pathogens in one study and the administration of sub-clinical griseofulvin doses in both studies likely resulted in an overestimate of terbinafine’s superiority. In a single trial employing the recommended dose of griseofulvin (1000 mg daily) mycological response was similar between terbinafine and griseofulvin (88% vs 82%, respectively); however, clinical response at the end of study was greater with terbinafine (81% vs 62%). Not surprisingly time to negative mycologic cultures was shorter for terbinafine (130 days vs 172 days).¹³¹

In three studies, traditional dose itraconazole (200 mg/day) was compared with traditional dose terbinafine (250 mg/day). In only one investigation where infections were solely restricted to those caused by dermatophytes did mycological cure rates favor terbinafine (81%–92% vs 63%–67%). In the remaining investigations no difference in mycological cure rates were observed between the allylamine and the triazole.^{132–134} The remainder of studies comparing the two agents examined pulse-dosing of itraconazole. In the treatment of distal and lateral subungual onychomycosis restricted to dermatophytes, no appreciable difference was observed between itraconazole (400 mg/day one week “on” three weeks “off”) and terbinafine (mycological cure rates: 75%–90% vs 76%–87%, clinical cure rates 53%–82% vs 50%–79%).^{135–138} Not surprisingly, itraconazole demonstrated superior cure rates among the non-dermatophyte moulds (62% vs 44%) and *Candida* species (92% vs 40%).¹³⁸ These studies are contradicted by a large multi-national trial wherein mycological cure rates at 18 months were significantly greater with terbinafine (76%–80%) than observed with pulse-dose itraconazole (38%–49%).¹³⁹ In selected subpopulations, complete cure rates observed after 4 years remained superior in the terbinafine arm (24%–78%) compared with those receiving itraconazole (24%–28%) as did mycological cure (46% vs 13%).^{140,141}

Finally, two investigations compare daily terbinafine with once weekly fluconazole (150 mg). Clinical cure rates (21%–38% vs 67%–81%), mycological cure rates (31%–51% vs 75–89%) and overall efficacy (31% vs 62%) were inferior in fluconazole treated patients.^{135,142}

Despite reasonable efficacy rates, the results of numerous trials indicate that a substantial fraction of onychomycosis patients treated with terbinafine remain uncured at the end

of treatment. Consequently several investigations have attempted to address whether additional intrinsic or extrinsic factors influence treatment response. Although the majority of these investigations were not adequately powered to definitively determine an association between selected covariates and treatment failure, several trends could be observed. The studies suggested that a higher fraction of patients 1) receiving lower terbinafine doses (125 mg vs 250 mg), 2) with distal and lateral subungual onychomycosis, 3) with big toenail involvement, or 4) with positive mycology 3 months into treatment remain uncured at the time of follow-up.^{143–145} The link between other factors such as demographic characteristics, the rate of nail growth, the species of infecting pathogen, the extent and duration of disease at the time of presentation and the number of nails involved remain unclear.^{144–146}

Tinea capitis

Ringworm of the scalp is a dermatophyte infection commonly seen among preschool and school-aged children. It is one of the few dermatophyte infections that does not adequately respond to topical therapy, often requiring 6 to 8 weeks of oral antifungal treatment.¹⁴⁷ Griseofulvin remains the gold standard in the management of this infection, but treatment failures are common and it is not unusual for children to remain on therapy for extended durations.¹⁴⁸

Several studies have examined the role of terbinafine in the treatment of tinea capitis; however, results need to be considered in the context of the geographic origin of the study participants given that the primary causative organisms and, thus response rates, are expected to vary between countries.^{149–151} The majority of these studies examine a weight-based dosing scheme with 62.5 mg of terbinafine administered to children under 20 kg, 125 mg administered to children between 20 and 40 kg and an adult dose of 250 mg administered to children over 40 kg.

With the administration of terbinafine for one week, *Trichophyton* infections are effectively treated in 56% of children.^{152,153} Efficacy rates ranged from 69% to 86% after 2 weeks of treatment, averaged 65% with 4 weeks of treatment and ranged from 80% to 100% after 6 weeks of therapy.^{44,152–155} Corresponding mycological cure rates observed after 1, 2, 4 and 6 weeks of treatment were 60%, 76%, 72% and >90%, respectively.^{44,152,154} By contrast, infections with *Microsporum* are less responsive to terbinafine. Response rates as low as 15% are observed with 1 to 2 weeks of therapy.¹⁵³ However, extended durations of treatment and/or doubling of the dose appeared to improve the likelihood of efficacy in children harboring *Microsporum*

and clinical and mycological response rates begin to approximate those observed for *Trichophyton*.^{153,156–158}

In comparative trials, terbinafine, when used for durations of 4 weeks, appeared to be as effective as griseofulvin administered for slightly longer intervals (8 weeks). Clinical and mycological cure rates ranged from 64% to 93% and 70% to 93%, respectively for terbinafine and 67% to 80% and 72% to 88%, respectively for griseofulvin.^{159–161} As above, the exception lies with infections caused by *Microsporum* where griseofulvin appears to be superior to terbinafine even when the allylamine is administered for 12 weeks.^{160–162} Pulse regimens wherein the standard dose or double the standard dose of terbinafine is administered daily for 1 week (followed by 3 weeks off) do not appear to confer any advantage or disadvantage in the treatment of *Microsporum* infections over standard regimens.¹⁶³ By contrast, terbinafine appeared to be slightly more effective than both itraconazole and fluconazole in treating tinea capitis.¹⁶⁴ It should be noted that in a number of the aforementioned studies, the griseofulvin doses employed (as low as 6 mg/kg) were markedly lower than those recommended for use in clinical practice. Consequently, the studies may have underestimated the efficacy of griseofulvin.

A single publication is available detailing the results of two randomized-controlled trials that compared 6 weeks of treatment with the recently marketed terbinafine oral granule formulation (5–8 mg/kg daily) with griseofulvin (10–20 mg/kg daily) for the management of tinea capitis. The new formulation is designed to be sprinkled on foods thereby improving the reliability with which the drug can be administered to young children (>4 years of age). In these investigations, the complete cure rate observed with terbinafine was superior to griseofulvin in one trial (46% vs 34%) but not the other (44% vs 43%). Similarly mycological cure rates were significantly higher in trial 1 (62% vs 50%) but not in trial 2 (61% vs 60%). In affirmation of the results conferred in previously conducted trials, subgroup analyses in these trials revealed that terbinafine was significantly better than griseofulvin when children were infected with *Trichophyton tonsurans* whereas griseofulvin proved superior for the treatment of infections with *Microsporum canis*.¹⁶⁵ This multi-national study also reported greater efficacy among US vs non-US infections which was likely accounted for by the higher fraction of children in the US that are infected with *T. tonsurans*.

Non-dermatophyte infections

Although not within the scope of this review, we would be remiss not to point out the increasing utilization of terbinafine, alone and in combination, for the management of

non-dermatophyte infections. Despite its higher MIC to pathogenic yeast, topically administered terbinafine appeared effective for the management of tinea versicolor,¹⁶⁶ and orally administered terbinafine (250 mg twice daily) has been used successfully for the treatment of cutaneous candidiasis.¹⁶⁷ Given, however, that the majority of superficial *Candida* infections will respond to topical antifungals, the role of terbinafine in these infections remains unclear. A brief summary of additional non-dermatophyte infections wherein terbinafine has been utilized is provided in Table 3.

Adverse effects

Terbinafine has been extensively used with a relatively low incidence of reported adverse drug reactions. Clinical trials evaluating the efficacy of orally administered

terbinafine in both children and adults have noted adverse event rates in as high as 52%; however, less than 10% were attributed to the drug.^{165,182–184} Most terbinafine related adverse events are mild or moderate and include gastrointestinal complaints (eg, nausea, abdominal pain, vomiting, diarrhea), cutaneous eruptions, weight gain, appetite changes, headaches, and vertigo.^{43,152,165,185,186} Those adverse reactions involving the gastrointestinal system and skin are most commonly associated with discontinuation of therapy,^{165,186} with the risk of discontinuation estimated at 3.4%.¹⁸⁷

Serious adverse drug reactions, most commonly involving the liver and the hematologic system, are only rarely reported with terbinafine use (0.04%).¹⁸⁸ Hepatotoxicity ranging from mild transaminitis to fulminant liver failure has been

Table 3 Case-reports and open-label studies examining terbinafine use in non-dermatophyte infections

Organism	Site	Dosing regimen	Outcome	Reference
<i>Aspergillus</i> spp.	toenail	500 mg/day (pulse: 1 wk/mos) 3 months	clinical and mycological cure (88%)	168
<i>Aspergillus flavus</i>	muscle ^a	250 mg daily 13 weeks	resolution	169
<i>Aspergillus sydowii</i>	toenail	500 mg/day (pulse: 1 wk/mos) ^b 3 months	failure	128
<i>Aspergillus ustus</i>	skin ^a	not provided ^c 11 months	resolution	170
<i>Cladosporium carrionii</i>	skin	500 mg daily 4–12 months	cure or clinical improvement (83%–100%)	171, 172
<i>Curvularia lunata</i>	heart valve (endocarditis)	125 mg twice daily ^{d,e} 7 years	tissue mycologically negative	173
<i>Fonsecaea monophora</i>	skin	250 mg daily ^b 7–10 weeks	clinical and mycological cure	174
<i>Fonsecaea pedrosoi</i>	skin	500 mg daily 4–12 months	cure or clinical improvement (83%–100%)	171, 172
<i>Paecilomyces lilacinus</i>	cornea (keratitis)	250 mg once daily ^{b,c} 10–12 weeks	resolution	175, 176
<i>Paracoccidoides brasiliensis</i>	perineum/scrotum	250 mg twice daily 6 months	resolution	177
<i>Piedra hortae</i>	scalp	250 mg once daily 6 weeks	effective	178
<i>Phialophora parasitica</i>	disseminated ^a	125 mg twice daily 2 months	drug discontinued	179
<i>Sporothrix schenckii</i>	cutaneous/subcutaneous	250 mg twice daily range: 8–37 weeks	success	180, 181

Notes: ^aPatient immunocompromised or immunosuppressed; ^bConcurrent treatment with itraconazole; ^cConcurrent treatment with voriconazole; ^dConcurrent treatment with amphotericin B; ^eConcurrent treatment with ketoconazole.

reported as a consequence of oral terbinafine use. It is estimated that 2.2% of patients treated with terbinafine will experience changes in their liver function tests.¹⁸⁷ The onset typically occurs after 3 weeks of therapy and resolution can take as long as 3 months after discontinuation of the drug. While the majority of cases resolve following discontinuation of terbinafine, reports are available detailing patients that have progressed to liver transplantation and death.^{189,190} Notably, hepatic findings are not restricted to adults. An FDA review of the recently marketed terbinafine oral granule identified two cases, among 1042 children treated, of elevated transaminases leading to discontinuation of the drug.¹⁹¹ Terbinafine-induced acute autoimmune hepatitis has also been reported in a patient infected with hepatitis B virus.^{192,193}

Blood dyscrasias including leucopenia, agranulocytosis, neutropenia and pancytopenia represent the other primary group of severe adverse drug reactions reported with terbinafine use. Most cases occur between weeks 4 to 5 of therapy and resolve within a week after stopping the medication. One fatality has been reported in a 79-year-old female who developed septic shock while being treated for terbinafine induced agranulocytosis.¹⁹⁴ Among children receiving the new granule formulation, leucopenia and/or neutropenia was observed in 1.8% (19/1042) of the children treated.¹⁹¹

Severe dermatologic eruptions including toxic epidermolysis, acute generalized exanthematous pustulosis, and Steven's Johnson syndrome have also been associated with terbinafine use.¹⁹⁵ Recently, reports have also linked dermatomyositis and subacute cutaneous systemic lupus erythematosus to terbinafine.^{196,197} In one patient, a skin eruption presenting 4 weeks after the onset of therapy and occurring with the triad of fever, hepatic dysfunction and lymphadenopathy led investigators to conclude the presence of hypersensitivity syndrome. Resolution was experienced within 6 weeks of discontinuing the drug.¹⁹⁸⁻²⁰³

An adverse effect unique to terbinafine is altered taste perception. Although numerous case reports have been published, there exist no reliable estimates of this side effect in patients taking terbinafine.²⁰⁴⁻²¹⁰ Ageusia has taken up to 6 weeks to resolve, and was reported in association with loss of smell and discoloration of the tongue, in one patient each.^{208,210} Possible risk factors for developing terbinafine associated taste loss include an age greater than 65 years and a body mass index less than 21 kg/m².²¹¹ Notably, a singular trial comparing terbinafine with griseofulvin for the treatment of tinea capitis, reported

a change of eating habits in 4.7% and 5.5% of children, respectively. Whether, however, this was due to changes in taste perception is unknown.¹⁶⁵

Of note, fewer patients receiving terbinafine pulse therapy as compared with traditional dosing experience elevations in liver enzymes or taste disturbances; however, the overall percentage of patients discontinuing therapy for adverse events was comparable between dosing strategies.¹²⁴

While only a few reports exist, ocular side effects have been observed with oral terbinafine use.²¹²⁻²¹⁴ Bilateral anterior optic neuropathy with decreased vision and optic disc edema was reported in a patient 2 weeks after starting terbinafine (500 mg/day).²¹⁴ After discontinuing the medication his vision improved. Anterior uveitis was reported in a second patient with acquired immune deficiency syndrome after 12 days of therapy. As in the previous case, symptoms resolved with discontinuation of terbinafine.²¹³

Among patients treated with topical terbinafine preparations, adverse events are primarily restricted to mild to moderate local skin reaction which may occur in as many as 6% of patients.⁹⁹

Conclusions

Terbinafine is among the most commonly used antifungal agents for the treatment of dermatophyte infections of the skin and nails. The success experienced by this drug can, in large part, be attributed to its favorable mycologic and pharmacokinetic profiles. Terbinafine possesses many of the characteristics required of a drug used for infections where clinical resolution is largely dependent on the slow turnover of infected tissue, namely, excellent penetration at the site of infection and sustained fungicidal activity for extended durations after the discontinuation of therapy. Numerous clinical trials corroborate the suitability of terbinafine for the treatment of dermatophytoses with efficacy rates comparable to or greater than existing antifungals despite shorter treatment durations. While the role of terbinafine use in systemic mycoses has been limited to date, the agent may eventually find utility as an adjunctive agent in the management of recalcitrant infections. Although terbinafine is likely to remain the first-line agent for a number of dermatophyte infections, prescribers should remain cognizant of the infrequent but severe adverse reactions that have been observed (eg, agranulocytosis, hepatotoxicity) and the potential for significant drug-drug interactions with medications that rely on CYP2D6 as a primary route of metabolism.

Disclosures

The authors disclose no conflicts of interest.

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