Terbinafine

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Terbinafine is an oral and topical antifungal agent in the allylamine class of antifungal compounds [1]. Discovered in 1983, it is closely related to naftifine. It became available in Europe in 1991, and in 1996 in the United States. Terbinafine is the only oral allylamine available in the United States and is used largely for the treatment of superficial fungal infections, especially those due to dermatophytes. There has been significant interest in developing the drug for the treatment of deep mycoses, either alone or in combination, for disorders such as cryptococcosis, invasive aspergillosis, and other mould infections, but there are only scant clinical data evaluating its efficacy in these settings. Terbinafine is a valuable antifungal drug for the treatment of superficial fungal infections, and has potential as an adjunctive agent in the treatment of selected deep mycoses.

Pharmacodynamics

Mechanism of Action

The mechanism of action of terbinafine is through inhibition of the synthesis of ergosterol, a key sterol component in the plasma membrane of the fungal cell [1, 2]. Terbinafine inhibits squalene epoxidase, the enzyme which catalyzes the conversion of squalene to squalene-2,3 epoxide, a precursor of lanosterol, which in turn is a direct precursor of ergosterol [3, 4]. A deficiency of ergosterol is detrimental to the integrity of the cell membrane resulting in a fungistatic effect similar to that seen with the azole antifungal compounds. In addition to this action, terbinafine also causes excessive intracellular accumulation of squalene, which is believed to exert a further toxic effect on susceptible fungal cells, thereby exerting a fungicidal effect [5]. In this regard, the mechanism of action of terbinafine is distinct from that of the azoles even though both compounds inhibit ergosterol biosynthesis through interruption of the synthesis of its precursors. Terbinafine has a strong affinity for fungal cell enzymes, but unlike the azoles, terbinafine has a very low affinity for the human cytochrome P-450 family of enzymes [6, 7]. This low affinity for the mammalian P-450 enzymes probably accounts for the favorable adverse event profile of terbenafine and the relatively few drug–drug interactions.

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Antifungal Spectrum

Terbinafine is a very broad spectrum antifungal agent, exhibiting the best activity against the dermatophytes of all the antifungal agents [8–12]. Terbinafine also demonstrates meaningful in vitro activity against many *Aspergillus* species including *A. fumigatus*, *A. flavus*, *A. niger*, and *A. ustus* [10, 13–15]. Other moulds that appear susceptible based on in vitro testing include many of the dematiaceous fungi such as *Fonsecaea* and *Cladophialophora* species [16] and the agents of eumycetoma [17]. Single case reports of successful therapy with terbinafine in patients with disseminated *Phialophora parasitica* [18], subcutaneous *Exophiala jeanselmei* [19], and *Curvularia lunata* endocarditis [20] suggest clinically relevant antifungal activity against these dematiaceous pathogens. Terbinafine does not consistently demonstrate significant in vitro activity against the hyaline moulds such as *Fusarium* species, *Paecilomyces* spp., *Scedosporium* spp., *Scopulariopsis* spp., or the zygomycetes, but there are reports of successful therapy with terbinafine alone or in combination with other antifungal agents for many of these pathogens [21–25]. The in vitro activity of terbinafine versus selected dermatophytes and moulds is demonstrated in Tables 1–3.

Terbinafine demonstrates good in vitro activity against *C. neoformans* [16, 26], but it has relatively poor activity against other yeasts, including many *Candida* species with

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Table 1 Minimum inhibitory concentrations of terbinafine against selected dermatophytes

Organism	MIC range (μg/mL)
Epidermophyton floccosum	0.001–0.05
Microsporum audouinii	0.001–0.04
Microsporum canis	0.0001–0.1
Microsporum gypseum	0.003–0.04
Microsporum persicolor	0.002–0.003
Trichophyton mentagrophytes	0.0001–0.05
Trichophyton mentagrophytes var. *interdigitale*	0.002–0.005
Trichophyton rubrum	0.001–0.15
Trichophyton simii	0.1–0.25
Trichophyton tonsurans	0.003–0.25
Trichophyton violaceum	0.001–0.1
Trichophyton verrucosum	0.001–0.006

MIC, minimum inhibitory concentration

Table 2 Minimum inhibitory concentrations of terbinafine against selected filamentous fungi

Organism	MIC range (μg/mL)
Acremonium spp.	0.25–8
Aspergillus flavus	0.01–1
Aspergillus fumigatus	0.02–5
Aspergillus nidulans	0.02–0.5
Aspergillus niger	0.005–2.5
Aspergillus terreus	0.04–5
Aspergillus ustus	0.1–0.5
Fusarium moniliforme	0.5–10
Fusarium oxysporum	0.25–20
Fusarium solani	1–128
Mucor spp.	64–128
Paecilomyces spp.	1–64
Penicillium spp.	1–5
Pseudallescheria boydii	10–64
Rhizopus spp.	64–100
Scopulariopsis brevicaulis	0.5–8

MIC, minimum inhibitory concentration

the exception of *C. parapsilosis* [27, 28]. Moreover, terbinafine is fungistatic against all of the *Candida* spp. Table 4 summarizes the in vitro activity against selected yeasts.

Terbinafine demonstrates excellent activity against some of the dimorphic fungi, including *Sporothrix schenckii*, against which it exhibits MICs comparable to some of the azole antifungal compounds, including itraconazole [8, 16]. In vitro activity against other dimorphic fungi, such as *Blastomyces dermatitidis*, *Histoplasma capsulatum*, and *Coccidioides* species is good [10, 16]. There are few in vitro or clinical data concerning the use of terbinafine against the other dimorphic fungi, *Penicillium marneffei* and *Paracoccidioides brasiliensis*. The in vitro susceptibility data for these dimorphic pathogens are shown in Table 5. Finally, terbinafine combined with amphotericin B, caspofungin, and selected azoles demonstrates modest additive or synergistic in vitro activity against *Pythium insidiosum* [29–31].

Table 3 Minimum inhibitory concentrations of terbinafine against selected dematiaceous fungi

Organism	MIC range (μg/mL)
Alternaria alternata	0.6–5
Cladophialophora bantianum	0.012–1
Cladosporium carrionii	0.04–1.25
Curvularia lunata	0.2–2
Curvularia fallax	0.25–0.5
Dactylaria constricta	0.01–0.03
Drechslera rostrata	10
Exophilia jeanselmei	0.06–2.5
Fonsecaea compacta	0.04
Fonsecaea pedrosoi	0.04–0.13
Madurella mycetomatis	0.01–1
Madurella grisea	0.01–2.5
Madurella spp.	1–4
Phaeoannellomyces werneckii	0.04–4
Phialophora verrucosa	0.04–0.13
Phialophora parasitica	0.1
Wangiella dermatitidis	0.001–0.08

MIC, minimum inhibitory concentration

Table 4 Minimum inhibitory concentrations of terbinafine against selected yeasts

Organism	MIC range (μg/mL)
Candida albicans	0.03–128
Candida glabrata	10–128
Candida guilliermondii	0.8–128
Candida humicola	1
Candida kefyr	0.5–50
Candida krusei	10–100
Candida parapsilosis	0.03–10
Candida tropicalis	1.2–128
Cryptococcus laurentii	0.08–0.6
Cryptococcus neoformans	0.06–2
Malassezia furfur	0.06–80
Rhodototula rubra	2.5–5
Trichosporon asahii	0.5–128

MIC, minimum inhibitory concentration

Table 5 Minimum inhibitory concentrations of terbinafine against selected dimorphic fungi

Organism	MIC range (μg/mL)
Blastomyces dermatitidis	0.04–1.25
Coccidioides species	0.3–0.6
Histoplasma capsulatum	0.04–0.2
Paracoccidiodes brasiliensis	0.04–0.16
Sporothrix schenckii	0.05–2

MIC, minimum inhibitory concentration

Pharmacokinetics

Oral

Terbinafine for systemic use is only formulated for oral administration. There is no intravenous formulation, in part

due to the drug's significant lipophilicity. Terbinafine is well-absorbed following oral dosing with at least 80% bioavailability [32, 33]. The drug demonstrates linear kinetics over a broad range of therapeutic doses with a proportional increase in the area under the curve (AUC) with increasing dose. Peak serum concentrations are achieved within 2 h following oral administration in both adults and children, although at similar doses, peak concentrations are somewhat higher in adults than in children [34]. Peak concentrations in adults following a 125 mg (2 mg/kg) dose range from 0.3 to 0.9 μg/mL, whereas the same dose in children (125 mg or 5 mg/kg) yields peak concentrations ranging between 0.4 and 1.0 μg/mL [34]. Absorption does not appear to be influenced by coadministration of food, antacids, most H-2 receptor antagonists, or proton pump inhibitors. Coadministration with rifampin may, however, significantly increase clearance, and cimetidine can cause a 33% decrease in clearance of terbinafine [7].

The drug is lipophilic and highly bound to plasma proteins (95%), and achieves its highest concentrations in adipose tissue and the keratinous tissues of the skin, nails, hair, and in sebum [35]. Concentrations in these tissues may be tenfold higher than simultaneous levels found in plasma. Because of the unique affinity of terbinafine for keratinous tissue, therapeutic levels can be found in stratum corneum, hair, and nails for up to 12 weeks following discontinuation of therapy. Moreover, measurable concentrations of terbinafine may be found in nail clippings up to 10 months following discontinuation of a limited course (1–4 weeks) of terbinafine [35, 36]. Among the antifungal agents, only itraconazole possesses this unique affinity for keratinous tissue and demonstrates similarly prolonged levels in skin and nails.

Metabolism is primarily hepatic, and at least 15 metabolites have been identified, although none of these demonstrate significant anti-fungal activity [37]. Approximately 80–85% of terbinafine metabolites are excreted in the urine and 15–20% are excreted in the bile. The elimination half-life in normal adults is approximately 26 h [38]. Among patients with significant renal or hepatic dysfunction, drug elimination may be delayed [34]. Accordingly, it has been suggested that the dosing amount be reduced by 50% without altering frequency of administration among patients with either significant renal or hepatic dysfunction.

Topical

Topical terbinafine is widely available as an over-the-counter preparation for milder forms of dermatomycosis and onychomycosis. It is not absorbed systemically in any measurable quantity, but significant levels are achieved in the stratum corneum and the nails although these levels do not approach those achieved with oral terbinafine [39, 40].

Dosing and Administration

Terbinafine is available in 250 mg tablets and in a topical 1% ointment. Because of its extended half-life with oral administration (approximately 26 h), the drug can be dosed once daily. When higher doses (≥1,000 mg per day) are given, it is recommended to split the daily dose to limit gastrointestinal disturbances. Topical therapy is administered twice daily. Duration of therapy for oral terbinafine is dependant on the condition being treated. For most cases of onychomycosis, courses of 3 months may be successful, although courses from 6 to 12 months may be necessary to achieve a lasting response [41]. For sporotrichosis, courses of 3–12 months have been used successfully for patients with uncomplicated cutaneous disease [42, 43]. For other invasive mycoses, few data are available concerning length of oral therapy.

Clinical Uses

Onychomycosis

The term *tinea unguium* refers to nail infections caused by typical dermatophytes whereas *onychomycosis* refers to the broader category of nail, infections that also includes nondermatophytic fungi and yeasts. There is considerable clinical overlap in these two entities and few clinical clues to distinguish from among the wide assortment of causative agents [44]. Several open-label and placebo-controlled studies have been performed to evaluate oral terbinafine for the treatment of onychomycosis [41, 45]. Mycologic response rates for toenail infections treated with terbinafine, 250 mg daily, range between 82% and 92% among patients given 3–6 months of therapy [46, 47]. Clinical cure rates are slightly less than mycologic response rates. For fingernail infections, response rates of 70% at 3 months of therapy and 100% at 6 months have been achieved [48–53]. Surgical or chemical removal of the nail in conjunction with oral terbinafine does not appear to enhance the efficacy of terbinafine alone for onychomycosis [54].

Based on results of comparative trials, terbinafine demonstrates greater efficacy than griseofulvin for both fingernail and toenail onychomycosis [41, 47, 55, 56]. Given the availability of safe and more effective preparations such as terbinafine and itraconazole, griseofulvin has largely fallen into disuse, having been superceded by these two newer oral antifungal agents. Studies comparing itraconazole 200 mg

daily and terbinafine 250 mg daily administered for 3 months suggest similar efficacy. These compounds are associated with mycologic cure rates ranging from 67% to 92%, and clinical cure rates from 63% to 80% [41, 45, 57].

Tinea Capitis

Tinea capitis, usually caused by *Trichophyton tonsurans*, is unique among the dermatophytoses in that it does not usually respond to topical antifungal therapy. Terbinafine has potent in vitro activity versus *T. tonsurans* [58]. Accordingly, oral terbinafine has been evaluated for the treatment of children with tinea capitis, effecting clinical cure rates of 80–100% and mycologic cure rates between 90% and 100% [34, 59, 60]. Compared to griseofulvin in randomized, double-blind studies, clinical cure rates are generally higher with terbinafine (90% vs 80%). Mycologic cure rates are similar [41].

Other Superficial Mycoses

For other superficial dermatophyte infections such as tinea corporis, tinea cruris, tinea imbricata, and tinea pedis due to a variety of dermatophytes including *Trichophyton rubrum*, *T. mentagrophytes*, *Microsporum canis*, and *Epidermophyton floccosum*, oral terbinafine is quite effective, but for most patients with these conditions, topical therapy can be used with excellent results. Ordinarily, for patients with superficial mycoses not involving nails and/or scalp, topical therapy with terbinafine is an appropriate alternative to systemic antifungal therapy with terbinafine or itraconazole.

Sporotrichosis

Among the deep mycoses, there has been the most experience with terbinafine for the treatment of sporotrichosis, and there have been limited reports of success with terbinafine at daily doses as low as 125 mg per day for 3–18 months [42, 61–63]. A large randomized double-blind trial compared two doses of terbinafine, 500 and 1,000 mg daily, administered for up to 24 weeks among 63 patients with cutaneous or lymphocutaneous sporotrichosis [43]. Mycological and clinical response rates were 87% with 1,000 mg daily and 52% with 500 mg daily. This success rate is not surprising given the significant concentration of terbinafine in the skin as well as excellent in vitro activity against *S. schenckii*. These response rates with terbinafine are similar to those with itraconazole for the treatment of cutaneous sporotrichosis [64].

Chromoblastomycosis

Chromoblastomycosis is a tropical fungal disease characterized by dense dermal fibrosis associated with organized granulomata. The agents of chromomycosis are typically dematiaceous (pigmented) fungi, and include such organisms as *Fonsecea pedrosoi* and *Cladosporium carrionii*. There has been sporadic use of terbinafine for patients with chromoblastomycosis [65]. In the largest study to date, 42 patients from Madagascar received terbinafine 500 mg daily for up to 1 year, and experienced 12-month mycologic and clinical cure rates of 85% and 74%, respectively [66]. While other experience with terbinafine for this disorder is limited to a small series of case reports [67–69], terbinafine appears to be a promising agent among patients with this very difficult to treat disease.

Fungal Mycetoma

There are at least 16 different fungal organisms that can cause fungal mycetoma. Terbinafine has been used sporadically at doses of 500 or 1,000 mg daily with some encouraging results [70]. For most cases of fungal mycetoma, a combined surgical and antifungal approach is necessary to achieve optimum response. No randomized and controlled studies for this disorder have been performed.

Other Endemic Mycoses

Terbinafine demonstrates excellent in vitro activity versus *H. capsulatum* and *B. dermatitidis*, and a few patients have received terbinafine for treatment of infections due to these organisms with encouraging results [70]. Terbinafine might be considered as potential salvage therapy among patients unable to tolerate any azole drug or amphotericin B. However, given the current availability of very effective azole compounds for these conditions, it is very unlikely that terbinafine will be studied prospectively for treatment of these mycoses.

Combination Therapy for Other Deep Mycoses

One potential use of terbinafine is for combination therapy with other approved antifungal agents for patients with cryptococcosis and invasive mould infections. In vitro data supporting the activity of terbinafine against *C. neoformans* led

to the use of terbinafine combined with fluconazole or amphotericin B in selected patients with acute CNS cryptococcosis. No significant drug–drug interactions have been observed and this combined therapeutic approach appears to be well tolerated. Prospective data assessing this approach have been not well documented.

Among patients with invasive mould disease, especially invasive aspergillosis [71], terbinafine has been an attractive potential agent for combination therapy with either amphotericin B or a triazole, such as itraconazole or voriconazole [72]. No prospective randomized studies have been done, but small series and sporadic case reports suggest a favorable response among highly selected patients with a combination of terbinafine with another antifungal agent, usually voriconazole [15, 73]. Up to 2,000 mg per day of terbinafine has been given successfully with stable clinical outcome and has been well tolerated [15, 70].

Adverse Effects

Oral terbinafine appears to be well tolerated in the vast majority of patients, and few drug–drug interactions occur. In the largest study of its kind, adverse effects were assessed in a postmarketing study involving 25,884 patients who had received terbinafine [74]. These data demonstrated that 10.5% of patients experienced a drug-associated adverse event. A more recent survey suggested a lower incidence of significant adverse events (2%) [75]. The most common side effects are gastrointestinal tract symptoms, including nausea, diarrhea, abdominal pain, and dyspepsia, which occurred in about 5% of patients. Skin disorders are the second most common adverse event, affecting fewer than 3% of patients. Most of the cutaneous adverse effects are benign rashes; however, several patients developed erythema multiforme [74], psoriasis [76], and generalized pustular eruptions [77, 78]. Hepatobiliary adverse events have been reported in fewer than 1% of patients and include cholestatic jaundice with mild to moderate hepatocellular dysfunction [79–83]. Terbinafine-induced hepatic failure requiring liver transplantation has been reported [84]. Less commonly reported adverse events include neutropenia [85–87], thrombocytopenia [88], toxic epidermal necrolysis [89], angioedema [74], bullous pemphigoid [90] cutaneous lupus erythematosus [91–94], dermatomyositis [95], and optic atrophy [96].

Despite the frequent concomitant use of other medications, including immunosuppressive agents as well as any other systemic antifungal compounds, terbinafine is an uncommon cause of significant drug–drug interactions [2, 7, 97]. The lack of interaction of terbinafine with the mammalian cytochrome P-450 enzyme system is believed to be responsible for this important characteristic. Unlike the azole antifungal compounds, terbinafine does not appear to significantly alter the metabolism of cyclosporine, tacrolimus, or sirolimus.

Summary

Terbinafine is a broad spectrum oral and topical antifungal agent that possesses a unique mechanism of activity distinct from other available systemic antifungal agents. Most clinical experience with this antifungal has been in the treatment of onychomycosis and other superficial fungal infections, but there is a growing body of experience with terbinafine for the treatment of deeper mycoses, especially cutaneous and lymphocutaneous sporotrichosis. The potential for use of terbinafine as a combination agent with another antifungal drug for the treatment of cryptococcosis and invasive mould disease is intriguing, but remains largely unexplored.

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