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Review Article

Terbinafine Preferred Antifungal with a Focus on Dermatophytes (A Review)

Mayank Panday[1]*, Divya Pandey[2], Prashant Upadhyay[2] and Sukirti Upadhyay[2]

[1]*School of Pharmaceutical Science, IFTM University, Moradabad, India*

[2]*School of Pharmacy, Oriental university, Indore, India*

***Corresponding Author:** Mayank Panday, School of Pharmaceutical Science, IFTM University, Moradabad, India.

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Abstract

17 years ago, Terbinafine was hailed in the global drug market to use as antifungal. In the treatment of superficial dermatophytosis terbinafine is become the first choice of drug, because of its effective mode of action, pharmacologic action and microbiologic profiles. Appropriate use of terbinafine as a topical and systemic drug needs to be used with appropriate guidelines. Terbinafine is primarily indicated and also discussed a contraindication for the treatment of non-dermatophyte infections. Terbinafine act by inhibiting the enzyme squalene epoxidase which is an important component of fungal cell membrane resulting in disintegration of fungal cell was allowing terbinafine to exert its fungicidal action. As per the recent advancement significant clinical relevance seen in activity of terbinafine when used in combination of other antifungal leads to decrease in resistance. This article reviews mode of action, antimycotic spectrum and disposition profile of terbinafine. we have also done a comparative analysis of terbinafine over other antifungals (griseofulvin, itraconazole, fluconazole) in the management of dermatophytes infection.

Keywords: Tinea; Trichophyton; Microsporum; Allylamine; Antifungal

Introduction

In 2008, the Oral terbinafine market has completed 12 years in the United States and 17 years globally. Terbinafine is sold in India as Terboderm by Omega Pharma and Tyza (Abbott Healthcare), Terbinafine first became available in Europe in 1991 and in the United States in 1996. The U.S. Food and Drug Administration has approved the first generic versions of prescription Lamisil (terbinafine hydrochloride) tablets. Since its launch, terbinafine has marked the first choice of all slots among oral and topical formulations. It is estimated to have captured nearly 80% of the greater than US$1.5 billion worldwide onychomycosis market (the reason for making up to the majority of prescription for children's) [1,2]. In current situations of fungal infections terbinafine remains the only commercially available orally allylamine and shares the topical allylamine/benzylamine market with naftifine, butenafine and amorolfine. In past few years several new formulations have been added to the portfolio of this antimycotic group of treatment. In September 2007 the US Food and Drug Administration also approved an oral granule in the paediatric age group. With the formulation which is available in the non-US market globally like systemic formulation and topical solution.

This article will review the 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 dermatophytosis with a brief discussion on the role of terbinafine in dermatophyte infections with the guidelines for appropriate dosage uses.

Superficial infections are mainly caused by keratinophilic fungi (keratin loving fungi) they are present on our stratum corneum nails, and hair. *Trichophyton, Epidermophyton*, and *Microsporum* species. Tinea corporis and tinea cruris is the dermatophytosis of glabrous skin and groin.

In localized infection, topical preparation is the preferred formulation which has good bioavailability and penetration for the localized area. They do not affect the first pass metabolism and kill the fungal infections on topical sites and reduce the side effect and chances of drug-drug interactions. It helps patient's compliance, increases chances of good outcomes [3].

Among all the antifungals the terbinafine has chosen to the first line of treatment because of its unique pharmacological and My-

cology action. It inhibits the squalene epoxidase, thereby inhibiting ergosterol action. In the past few years, the humid and hot climate helpful for the cause of dermatophytes infection and the terbinafine is consistently active against antifungals with a 90% fungicidal rate in 250 mg once daily dose of terbinafine up to 2 weeks [3,4]. Currently, there are clinical failures and relapse cases are higher with terbinafine [5,6]. One of the principle reasons in the relapse of antifungals are decreased when the concentration increase in some relapse cases of dermatophytes infection up to 500 mg once daily [7,8].

Itraconazole is a group of antifungals which comes in an azole group and this drug molecule inhibit the cytochrome P450 enzyme and convert in lanosterol to ergosterol under demethylation. A 100 mg up to 2 weeks dose of itraconazole shows a significant reduction in dermatophytosis infection and higher concentration is required up to 7 days for the desired result and due to relapse cases [9,10]. In short interval dermatologists and physicians start using 200 mg once daily for a prolonged period [11,12].

Resistance of antifungal agents has been occurred widespread and used in conventional-dose with an increase in relapse rates promoting a need to find an effective first-line antifungal drug with lesser resistance and with a decrease in relapse rates. Hence, the present study was conducted to compare the efficacy of oral terbinafine versus itraconazole in the treatment of tinea corporis and tinea cruris.

Clinical mycology

Terbinafine discovered in 1983 and it is a member of the allylamine antifungals group. Due to the presence of tert-butyl acetylene substitution of the phenyl ring on the side chain of the molecule. The efficacy of oral terbinafine is increased 100 times in in-vitro studies of Naftifine [13,14]. Terbinafine interfere in the biosynthesis of fungi. By inhibiting the squalene epoxidase, it will stop the formation of ergosterol, with the help of these step squalene convert into 2,3-oxidosqualene (an ergosterol precursor). so ultimately the synthesis is stopped in lack of ergosterol and lead a cell death because of weak cell wall integrity. In-vitro study states that the terbinafine has minimal drug interaction and a small concentration inhibit 95% activity of squalene epoxidase [15-17].

In the clinical cases of dermatophytes terbinafine outcomes are observed and it found that the terbinafine is showing susceptibility to some organism including pathogenic yeast, thermally dimorphic fungi [18]. On other hand Terbinafine showing a wonderful activity in a reduction of some species, *Trichophyton, Microsporum* and *Epidermophyton.*

The minimum inhibitory concentration (MIC) of Drug terbinafine has observed very lower to kill the fungi including other species of dermatophytes comparatively with other antifungals which are also active against these organisms like triazoles, imidazoles, griseofulvin [19,20].

While resistance is very rare but the increased cases of antifungals show that the cross-resistance when it used with different antifungals [21]. When the terbinafine is used as a combination in the management of invasive mycoses. Against *Aspergillus fumigatus,* then indifference was observed that the combination of terbinafine and amphotericin. B, similarly, fluconazole, itraconazole including terbinafine did not improve the activity of *A. fumigatus.* Moreover, combination of triazole and terbinafine shows a synergy response (greater effect) on this pathogen [22]. In the management of invasive cases terbinafine showed an ultimate utility and it starts using as a most important agent.

Clinical pharmacology

Terbinafine is 70 to 80% absorbed from oral route and it shows a linear absorption towards the ideal dose (250 mg) of terbinafine and the total body exposure is directly proportional to dose. The percentage of absorption dose doesn't appear from children and defer in adults it always based on the per kilogram on body weight [25]. If the children are less than 6 years old it will give according to its body weight, and not recommended in less than 2 years old.

Topical based terbinafine cream and gel formulation absorption having a normal range of skin is 746 to 949 ng/cm. Within 7 days of application the concentration is increased in stratum corneum by 15% moreover AUC is also increased upto 40% under 1 week. It has been observed that in stratum corneum the topical preparation is well absorbed the resultant systemic exposure is several orders of magnitude lower than observed after oral terbinafine administration (Table 1 and 2).

Topical preparation is commonly used in the treatment of dermatophytes and the good bioavailability shows a great reduction in fungi, topical is used as the first line of therapy in the superficial skin infection. A great bioavailability and Efficacy of topical preparation will help to reduce the longer time of treatment. Moreover, the topical cream and gel sand other preparation are helping to minimize the side effect and chances of recurrence and increase therapeutic response [26].

Therapeutic uses

Terbinafine is recommended in the management and treatment of dermatophytosis (tinea cruris, capitis and tinea Corporis) and

Parameter	Adults 125 mg single-dose (n = 26)	Adults 250 mg single-dose (n = 29)	Adults 125 mg steady-state (n = 10)	Adults 250 mg steady-state (n = 22)	Children 125 mg single-dose (n = 28)
Tmax (h)	1.3 - 1.5	1.4 - 1.5	1.6	1.2	1.7 - 2.1
Cmax (ng/mL)	506 - 565	1340 - 1656	646	1700	706 - 909
AUC (h*ng/mL)	1624 - 2135	4740 - 6762	3720	10481	2967 - 4104
Cl/F (L/h/kg)	1.2	-	0.55	0.4	1.9
Vss/F (L/kg)	19.2	-	-		19.5
t1/2α (h)	0.7	0.35	-		1.2
t1/2β (h)	26.7	12.6-14.2	-		14.7
t1/2γ (h)	-	-	-	396	156

Table 1: Pharmacokinetic parameter estimated of terbinafine in oral administration.

Parameter	1% gel × 7 days healthy skin	1% cream 7 days
Stratum corneum Cmax (μg/cm^2)	0.91	0.94 - 2
Stratum corneum AUC (h*μg/cm^2)	12.7	11.7 - 13.5
Tissue t1/2 (h)	1.2	68
Plasma Cmax (ng/mL)	3.82	-
Plasma AUC (h*ng/mL)	63	-

Table 2: Local exposure of topical terbinafine application.

onychomycosis. Moreover, terbinafine is using on other pathogens including systemic mycoses other than the dermatophytes. Explore the utility of terbinafine to other infections, orally administered tablets of terbinafine are not effective on Pityriasis versicolor.

Cutaneous dermatophytes

There are number of species present in today's environment which is responsible to cause dermatophytes infection on face, groin, trunk, feet. For the treatment of these body areas topically will be the first line and if the case is found under widespread or chronic in nature systemic therapy will be preferable [27,28].

Tinea cruris: Is called as jock itch and it is most common in males due to occlusive garments, 1% terbinafine hydrochloride cream, gel formulation has shown a significant reduction on a lesion and impact on a mycological cure rate by 94% and clinically cure rate by 84% with this overall ranging rate upto 63% to 83%. Statically topical use of terbinafine gives an effective result in the management of fungal infection. Then a 2- week treatment of 2% ketoconazole cream [29-33].

Tinea pedis: Due to the lack of sebaceous gland secretion over sole and its web spaces make them very favorable to such infection. Reason of leading chronicity of infection are increased sweating, occlusive footwear use of laden socks and the major causative pathogen which is responsible for tinea pedis are, *T. rubrum, T. mentagrophytes* and *E. floccosum.* 1% terbinafine cream, gel formulation was applied on the infected area and comparatively mycological cure rate 82% to 97% and efficacy rate 64% to 86%.

Onychomycosis

In simple words onychomycosis is an infection of the nail caused by dermatophyte, mold or yeast. Tinea ungunium is also referred to as dermatophyte infection of nail. Various clinical patterns of invasion are present in onychomycosis. The most common organisms are *T. mentagrophytes* and *T. rubrum,* and distal lateral subungual onychomycosis, the most common clinical type. So, in the treatment of onychomycosis includes both oral and topical with combination therapy of terbinafine and itraconazole as a pulse dosing gives satisfactory results with a period of 12 to 24 weeks in cases of fingernail or toenail. Respectively, in all the nail problems one-half is accounted by finger or toenail onychomycosis in this fungal infection nail became thickened, discoloured, or prone to splitting. Toenail infections are mostly caused by dermatophytes whereas over 50% of cases are caused by non-dermatophytes species [34-36].

Commercially available group of antifungals like griseofulvin, Terbinafine, itraconazole, are used in the management of such infections and it's efficacy is also dependent on the duration of course which is typically required in the treatment. There is a study rate of 12 months which is described below and the protected growth rate of nail including which drug remains in the affected nail. Af-

ter approval, numerous of studies are performed and evaluated based on dose regimens for the finger nail, toenail fungal infection with terbinafine 250 mg/day. With this dose clinical rate is 44% to 77% and Mycologic rate is 72% to 92% was recorded, respectively. Notably, there is a small difference found in patients who are treated in 12, 18 and 24 weeks. Moreover, fingernail onychomycosis comparatively shows a good response rate of 71% to 100% [37-42] when the daily dose of terbinafine 250 mg once in a day was given with topical preparation of amorolfine once daily gives more improvement in fungal infection response [43-47]. 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. 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. 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. 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 [48-51].

Non-dermatophyte infection

In the management of non- dermatophytosis infection the higher MIC is despite to pathogenic yeast. Topical application of terbinafine appears in the management of pityriasis versicolor and mainly caused by *Malassezia furfur.* Terbinafine is an orally administered terbinafine (250 mg twice daily) has been used successfully for the treatment of cutaneous candidiasis. Moreover, a summary and additional [52,53].

Adverse effect

In the treatment of dermatophyte, Terbinafine 250 mg/day evaluated with very low Chances of adverse drug reactions. In the clinical evaluation and on efficacy parameter systemic terbinafine in children and adults have noted as adverse event rate upto 52% and 10% with attribute with the drug. Most common adverse events are gastrointestinal irritation, nausea, vomiting, abdominal pain, weight gain, headache when higher doses are administered [61-66].

Organism	Dose Rate	Site	Recover Percentage	Reference
Sporothrix schenckii	250 mg twice a day upto 8-36 weeks	Cutaneous/ subcutaneous	Success	[59,60]
Piedra hortae	250 mg/day upto 6 weeks	Scalp	Effective	[58]
Fonsecaea monophora	250 mg/day upto 10 weeks	Skin	Cured	[57]
Cladosporium carrionii	500 mg/day- upto 12 months	Skin	83% to 100 %	[55,56]
Aspergillus sydowii	500 mg/day- 3 months	Toenail	Failed	[51]
Aspergillus spp	500 mg/day- 3 months	Toenail	88% clinical and Mycological	[54]

Table

The liver and hematologic system are most commonly involving rate of 0.04%, Hepatotoxicity ranging and the liver failure are the consequences which is very rarely reported with Terbinafine. Only 2.2% of patient has treated with Terbinafine has experienced the changes in liver function test [67]. Notably, a singular trial report comparing terbinafine with griseofulvin for the treatment of tinea capitis. 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 [54]. 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 [68].

With the use of terbinafine various ocular disorders have been observed with the use of terbinafine in a patient after two weeks the bilateral anterior optic neuropathy with decreased vision and optic disc edema was reported (500 mg/day). After discontinuing the medication, the vision improved. After 12 days of therapy Anterior uveitis was reported in a second patient with acquired immune deficiency syndrome. As in the previous case, symptoms resolved with discontinuation of terbinafine [69-71].

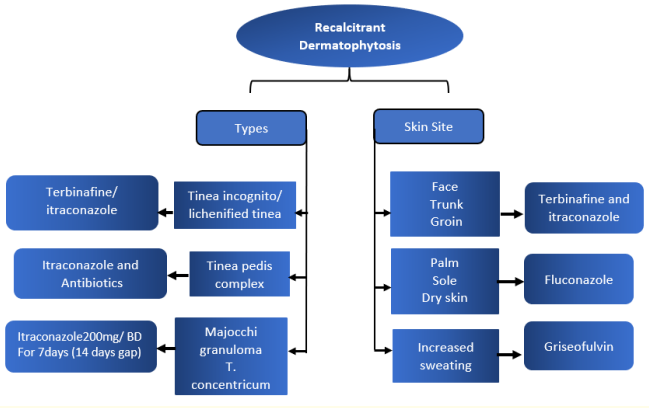
Among patients treated with topical terbinafine preparations, adverse events are primarily restricted to mild to moderate local skin reactions which may occur in as many as 6% of patients [72].

Dermatophytosis treatment

Treatment of recalcitrant dermatophytosis is dependent on their condition which are as follows:

- MIC level against skin pathogen.
- Secretion profile of drug.
- Concentration achieved at target site.

In the cases of dermatophytosis or recalcitrant dermatophytosis if the patient is not responding may be they have some immunity issue so the therapy will be planned accordingly. Which is provide in below figure [73].



Figure

Conclusion

In the cases of recalcitrant dermatophytosis Terbinafine is a preferred antifungal choice due to its fungicidal action of skin and nail and because of its characteristics to present in stratum corneum, sebum nails and hair for months after stopping the medication is likely responsible for the better treatment of dermatophytes and its kill the fungi at the same MIC and MFC so chances of drug to drug interactions are likely less and a preferred Choice for poly pharmacy patients. And numerous clinical trials are corroborating the suitability and efficacy are far better than the existing antifungals. While the treatment in dermatophytosis or a systemic mycosis has been limited to date, Moreover Terbinafine is still remain as a first line of treatment in most of the dermatophytosis infections 250 mg once daily is sufficient as per the IADVL guidelines. Infrequent but the severe adverse effect (Hepatotoxicity) and potential for the drug interactions for the medication that rely on CYP2D6 as a primary route of metabolism.so twice daily Terbinafine upto 4 week gives 80 to 100% result and its more effective than placebo in mycological cure and as well as clinical outcomes and reduces the risk of symptoms score, and over all efficacy.

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