Review Article

Newer Topical Treatments in Skin and Nail Dermatophyte Infections

Kanika Sahni, Sanjay Singh, Sunil Dogra[1]

Department of Dermatology and Venereology, AIIMS, New Delhi, [1]Department of Dermatology, Venereology and Leprology, PGIMER, Chandigarh, India

Abstract

Dermatophytes are amongst the most common causative agents of fungal infections worldwide and widespread in the developing countries. Various studies have found the significantly rising trend of this infection in India especially in last 4-5 years. The growing epidemic of recurrent/chronic dermatophytosis has led to the need for newer antifungal agents and/or preparations. Furthermore, resistance to commonly used topical and oral antifungals has increased alarmingly. Significantly increasing resistance has led to state of anxiety in physicians and significant distress to the patients socially, emotionally, and financially. Newer formulations or newer derivatives of existing drug classes and few newer drug classes are being developed to tackle this menace. Other forms of local therapies including lasers and photodynamic therapy are still in developmental phase and still need to be optimized in terms of dosing schedule, frequency of use and duration of therapy. Moreover, cost of these therapies remained most important obstacle in developing countries like India. We are hereby reviewing the newer formulations of topical therapies and drugs/interventions in experimental phase.

Keywords: *Dermatophytosis, tinea, topical antifungal*

Introduction

Superficial fungal infections of the skin, hair, and nails are common worldwide with a prevalence of 20–25%, of which dermatophytes are the most common causative agents.[1] Dermatophytosis is defined as an infection of the hair, nails, or skin by the dermatophytes which include three genera i.e., *Trichophyton spp*., *Microsporum spp.*, and *Epidermophyton*. As dermatophytic infections of the hair mainly require systemic antifungal therapy, we will focus only on the topical therapy of dermatophytic infections of the skin and nails.

The most common clinical morphology is tinea corporis and cruris in most studies, and *Trichophyton rubrum* is the most commonly isolated species.[1,2] However, few studies have documented *T. mentagrophytes* as the most common isolate.[1,3,4] Recently, a study from a tertiary centre in New Delhi found *T. interdigitale* (56%) as the most common isolate followed by *T. tonsurans* (25.7%).[5]

Chronic and Recalcitrant Dermatophytosis

There is no standard definition of chronic dermatophytosis in literature. However, patients with disease duration of more than 6 months to 1 year, with or without recurrence, despite being treated with adequate course of antifungal drugs are considered as chronic dermatophytosis. Recurrent dermatophytosis is defined as reoccurrence of infection within few weeks of stopping the treatment.[6] Although there is sparse literature on the exact frequency of clinical resistance in the Indian subcontinent, it is being very commonly encountered in clinical practice. Adimi *et al*. assessed the efficacy of antifungal agents, i.e., griseofulvin, terbinafine, itraconazole, ketoconazole, fluconazole, voriconazole, clotrimazole, ciclopirox olamine, amorolfine, and naftifine over 15 different species of dermatophytes using Clinical and Laboratory Standards Institute (CLSI) broth microdilution method (M38-A). Itraconazole and terbinafine showed the lowest and fluconazole had the greatest minimum inhibitory concentration (MIC).[7] A study conducted in a Mexican hospital assessed *in-vitro* resistance among 36 patients using the E-test method who did not respond to treatment for dermatophytosis. One strain of *T. tonsurans* and three strains each of *T. rubrum* and *T. mentagrophytes* showed resistance to azoles. One *T. rubrum* strain was resistant to all three

How to cite this article: Sahni K, Singh S, Dogra S. Newer topical treatments in skin and nail dermatophyte infections. Indian Dermatol Online J 2018;9:149-58.

Received: October, 2017. **Accepted:** February, 2018.

Address for correspondence:
Dr. Sunil Dogra, Department of Dermatology, Venereology and Leprology, PGIMER, Chandigarh, India.
E-mail: sundogra@hotmail.com

Access this article online

Website: www.idoj.in

DOI: 10.4103/idoj.IDOJ_281_17

Quick Response Code:

azoles, i.e., itraconazole, ketoconazole, and fluconazole. All these seven dermatophyte strains were resistant to fluconazole.[8,9]

Various factors including host, agent, environmental, or topical corticosteroid abuse have been attributed for chronicity and recurrent dermatophytic infections in India.[6] Due to the increasing proportion of recalcitrant cases, there is an urgent need of newer topical and oral antifungal medications.

Treatment of dermatophyte infections

Besides pharmacotherapy, there are many important considerations while managing a case of dermatophytic infection. Improving hygiene of the skin, nails, and hair; avoidance of humidity and occlusive clothing; discontinuation of corticosteroid containing topical antifungal creams; and close examination of possible carriers, i.e., family members and pets, are important measures in the treatment.[10]

Role of Topical Antifungals

Treatment of dermatophytosis consists of oral or topical antifungal drugs or a combination of both, depending on the extent and severity, site of infection, and causative organism.[11] Topical antifungals are generally considered the first-line therapy for uncomplicated, superficial dermatomycoses owing to their high efficacy and low potential for systemic adverse effects. These drugs are compounded into various types of vehicles, i.e., creams, lotions, gels, or sprays to facilitate penetration and efficacy depending on the site of involvement. They readily penetrate the stratum corneum when applied to the skin surface, which leads to killing of the fungi or inhibition of their growth, achieving clinical and mycologic eradication. The main classes of topical antifungal drugs include the polyenes, the azoles, and the allylamine/benzylamines. Recently, various new antifungal drugs with increased efficacy and associated anti-inflammatory effect have been introduced in India and have broadened the armamentarium against this chronic dermatosis. A Cochrane review and meta-analysis found no significant differences among the topical antifungals in regard to clinical and mycological cure at the end of the treatment. However, terbinafine and butenafine led to sustained cure compared to clotrimazole.[1,12] Naftifine (1%) was found to be superior to placebo in terms of mycological cure rates, although the evidence was low. Combinations of azoles with corticosteroids were slightly more effective than azoles alone for clinical cure, but there was no statistically significant difference with regards to mycological cure.[13] This might be due to rapid improvement in inflammatory component and symptoms which leads to increased patient compliance also. However, inadvertent use of this combination therapy may be associated with treatment failure and adverse effects.[14] Recently, a specific cutaneous form, tinea pseudoimbricata, has been described after steroid abuse.[1]

The classification of important drugs is mentioned in Table 1. The development of new topical broad-spectrum antifungal agents has presented new treatment options for the management of superficial cutaneous mycoses, especially dermatophytosis, which has become a difficult to treat entity in this era. This article focuses on the newer topical antifungal drugs. Description of important drugs is presented below.

1. Azoles

Azole antifungals are composed of two chemically related groups, i.e., imidazoles and triazoles. Triazoles differ from imidazoles by having three nitrogen atoms in the azole ring whereas imidazoles has two. They act by blocking the lanosterol 14α-demethylase, an enzyme necessary for the biosynthesis of ergosterol. Ergosterol is the primary sterol derivative which is an essential component of the fungal cell membrane.[15] Decreased levels of ergosterol in cell membrane and accumulation of intracellular 14α-methylsterols lead to increased membrane rigidity, increased membrane permeability, disruption of membrane-bound enzymes, inhibition of growth, and ultimately cell death.[15] Various topical azoles, preparations, their uses, and frequency of application is described in Table 2.

Sertaconazole

Sertaconazole, an imidazole antifungal agent, has both fungistatic and fungicidal activity depending on the concentration of the drug and the specific organisms involved in the infection. At higher concentration, it directly binds to nonsterol lipids in the fungal membrane leading to increased permeability and rapid leakage of key intracellular constituents (e.g., adenosine triphosphate) to such an extent that immediate cell death ensues.[16,17] It has broad-spectrum antifungal activity against all three genera of dermatophytes, *Candida* and *Cryptococcus*. In addition, it is also effective against Gram-positive cocci.[16] Notably, this sensitivity was maintained in isolates of dermatophytes and laboratory strains of *Candida* that exhibited reduced susceptibility to other azoles. *In-vitro* and animal studies have proven anti-inflammatory and antipruritic effects of sertaconazole which leads to increased compliance. Sertaconazole 2% cream was approved by the FDA in 2003 for the treatment of tinea pedis caused by *T. rubrum, T. interdigitale*, and *Epidermophyton floccosum* in individuals aged 12 years or more.[18] The recommended dosage of 2% sertaconazole cream is applied once or twice daily for a period of 4 weeks.[16] Various newer topical formulations of sertaconazole, i.e., anhydrous gel, microsponge, microemulsion, nanovesicles, loaded hydrogel, bioadhesive gel, transdermal patch, and nail patch are under development to enhance the dermal delivery and skin retention of the drug.

Table 1: Classification and mechanism of action of antifungal antibiotics

Class	Drugs	Mechanism of action	Antifungal effects against dermatophytes
Azoles (Imidazoles)	Clotrimazole, Ketoconazole, Econazole, Bifonazole, Lanoconazole, Miconazole, Fenticonazole, Oxiconazole, Tioconazole, Sulconazole, Sertaconazole, Luliconazole, Eberconazole	Inhibition of fungal lanosterol 14-α demethylase resulting in depletion of ergosterol and accumulation of toxic sterols in the fungal cell membrane	Fungistatic/fungicidal
Azoles (Triazoles)	Fluconazole, Itraconazole, Efinaconazole		
Allylamines	Naftifine, Terbinafine	Interferes with synthesis of ergosterol by inhibiting squalene 2,3-epoxidase that is responsible to convert squalene to squalene oxide	Fungicidal
Benzylamines	Butenafine		
Hydroxypyridone	Ciclopirox, Rilopirox	Inhibition of essential enzymes by creating a large polyvalent cation through chelation, thus interfering with mitochondrial electron transport processes and energy production	Fungistatic/fungicidal (depending on dose and duration of exposure)
Morpholines	Amorolfine	Inhibition of C-14 sterol reductase and C-8 sterol isomerase in the ergosterol synthesis pathway	Fungicidal/fungistatic
Thiocarbamates	Tolnaftate, Tolciclate	Inhibit the conversion of squalene to 2,3-oxidosqualene by the enzyme squalene epoxidase	Fungicidal
Echinocandins	Anidulafungin, Micafungin, Caspofungin	Fungal (1,3)-glucan synthase inhibition resulting in depletion of cell wall glucan and osmotic instability	Fungicidal/fungistatic
Polyenes	Liposomal Amphotericin	Binds with ergosterol leading to formation of aqueous channels, increased membrane permeability and subsequent leakage of intracellular contents	Fungicidal
Oxaboroles	Tavaborole	Inhibits cytoplasmic leucyl-transfer RNA synthetase, interfering with fungal protein synthesis	Fungicidal
Newer investigational drugs	ME1111	Inhibits succinate dehydrogenase enzyme (complex II), a critical enzyme involved in mitochondrial respiratory electron transfer	Fungicidal
Miscellaneous	Xianglian, ajoene, triclosan, eucalyptus oil, dermcidin, macrocarpal C, tetrandrine		

Luliconazole

Luliconazole, R-enantiomer of lanoconazole, is an imidazole antifungal agent.[19] It has been found that the MIC for luliconazole is 1–4 times lower than lanoconazole and terbinafine for *T. rubrum* and *T. mentagrophytes* strains.[19] Luliconazole 1% has also been found to successfully eradicate dermatophytic infection caused by *T. mentagrophytes* in experimental model in half the time or less required for 1% terbinafine cream and bifonazole 1% cream.[18] Besides dermatophytes, *in-vitro* studies have documented the effectiveness of luliconazole against *Candida*, *Malassezia* subspecies, and *Aspergillus fumigatus*.[19] Luliconazole was approved by the FDA in November 2013 for the treatment of tinea pedis, tinea cruris, and tinea corporis. The recommended dosage of 1% luliconazole is once daily for 1 week for tinea cruris and tinea corporis and 2 weeks for tinea pedis over affected area(s) and immediate surrounding area(s).[19] Recently, the role of luliconazole is being explored in the management of onychomycosis. It has excellent penetration capability through the nail layer.[19] A multicenter, double-blind, randomized study using once daily luliconazole 5% nail solution in cases with distal lateral subungual onychomycosis with 20–50% clinical involvement have found good efficacy and tolerability.[20] Jones *et al*. assessed

Table 2: Formulations and use of individual topical antifungal drugs

Drug	Conc. of drug (%)	Preparations	Frequency of application	Additional remarks
Azoles (Imidazoles)				
Clotrimazole	1, 2	Cream, gel, lotion, solution, powder	BD	
Ketoconazole	2	Cream, lotion, shampoo, soap, powder	OD	
Econazole	1	Cream	OD-BD	
Bifonazole	1	Cream	OD	
Lanoconazole*	1	Cream, ointment, solution	OD	Anti-inflammatory activity and wound-healing property
Miconazole	1	Cream, lotion	BD	
Fenticonazole*	2	Cream, spray, powder	BD	Antibacterial and antiprotozoal activity
Oxiconazole	2	Cream, lotion	OD-BD	
Tioconazole	1	Cream	BD	
Sulconazole*	1	Cream, solution	BD	
Sertaconazole	2, 5	Cream, lotion, shampoo, powder	BD	Anti-inflammatory and anti-itch activity
Luliconazole	1	Cream	OD	
Eberconazole	1-2	Cream, lotion, shampoo, powder, gel	OD-BD	Antibacterial and anti-inflammatory property
Triazoles				
Fluconazole	0.5, 1, 2	Cream, lotion, shampoo, powder, gel	OD-BD	
Itraconazole	1	Cream	OD-BD	
Efinaconazole*	10	Solution	OD	
Allylamines				
Terbinafine	1	Cream, gel, lotion, solution, powder	OD-BD	
Naftifine*	1-2	Cream, gel	OD-BD	Anti-inflammatory activity
Benzylamines				
Butenafine	1	Cream	OD-BD	Anti-inflammatory activity
Hydroxypyridone				
Ciclopiroxolamine	1	Cream, Lacquer	BD, Lacquer as once or twice weekly	Antibacterial, antiparasitic (against Trichomonas) and mild anti-inflammatory activity
Morpholines				
Amorolfine	0.25	Cream, Lacquer	BD	Anti-bacterial activity against Actinomyces
Oxaboroles				
Tavaborole*	5	Solution	OD	
Polyenes				
Liposomal Amphotericin B	1	Gel	BD	
Tolnaftate	1, 2	Cream, ointment, lotion	BD	
Whitfield's ointment	3% salicylic acid and 6% benzoic acid	ointment	TDS	
Griseofulvin	1	Solution, ointment, cream	OD	
Tetrandrine*	2	Cream	BD	
Xianglian*	5.58-10, 22.3-30	Cream, lotion	OD-BD	
Ajoene*	0.6	Gel	BD	Antimycobacterial and antibacterial activity
Triclosan	0.03-1	Soap	OD	Antibacterial and antiviral activity

*Not available in India, BD: twice daily, OD: once daily

safety and tolerability of 10% luliconazole solution in patients with moderate-to-severe distal subungual onychomycosis and found significant accumulation of the drug in the nail with minimal systemic exposure.[21] Another randomized controlled trial compared fractional carbon dioxide (CO_2) laser combined with luliconazole 1% cream to fractional CO_2 laser for the treatment of onychomycosis and found significantly higher efficacy in the former.[22]

Eberconazole

Eberconazole, an imidazole azole, has been found to have broad antimicrobial activity. It has shown good efficacy against dermatophytes, *Candida*, and *Malassezia furfur*. Similar to sertaconazole, it also possesses antibacterial property against Gram-positive bacteria.[23] It has anti-inflammatory activity similar to aspirin and ketoprofen, and this effect has been attributed to the inhibition of 5-lipooxygenase and to a lesser extent of cyclooxygenase-2.[23] A randomized controlled trial found the efficacy and safety of 1% eberconazole nitrate cream similar to that of 1% terbinafine hydrochloride cream in the treatment of localized (<20% involvement) tinea corporis and tinea cruris.[24] Recently, a study used ethyl cellulose microsponges as topical carriers of eberconazole nitrate and found four-fold higher retention of eberconazole nitrate in the stratum corneum layer compared with commercial cream,[25] which might lead to increased efficacy of the drug.

Lanoconazole

Lanoconazole, a racemic imidazole antifungal agent, has been widely used in Japan for management of tinea pedis, tinea corporis, and cutaneous candidiasis.[26] Uratsuji *et al*. documented the anti-inflammatory activity of lanoconazole by inhibition of IL-8.[27] In addition, it has been found to accelerate wound healing in animal models, however, the relevance of this feature in the management of dermatophytosis is yet to be addressed.[26] An animal model study showed lower efficacy of lanoconazole compared to terbinafine and luliconazole.[28] Once daily local application is currently recommended at affected sites. Occasionally, it can cause allergic contact dermatitis.[26]

Efinaconazole

Efinaconazole is a newer emerging triazole antifungal effective against dermatophytes, *Candida species*, and nondermatophyte molds. Efinaconazole 10% topical solution got FDA approval for the topical treatment of toenail onychomycosis caused by *T. rubrum* and *T. mentagrophytes* in June 2014.[29] It is to be applied once daily for 48 weeks with the help of a brush applicator to the affected toenail and its undersurface, nail folds, nail bed, and hyponychium.[29] The drug reaches the site of infection by both transungual delivery and spreads through the subungual space. It is deactivated by keratin to a lesser extent compared to other azoles.[19,29,30] Sugiura *et al*. compared the keratin affinity of efinaconazole to amorolfine and ciclopirox. Efinaconazole was found to penetrate the nail bed to a greater extent (14.3% efinaconazole vs 0.7% and 1.9% for ciclopirox and amorolfine in keratin suspensions, respectively). Moreover, it inhibited the growth of *T. rubrum* more than ciclopirox and amorolfine whereas its efficacy against *T. mentagrophytes* was similar to amorolfine and better than ciclopirox.[30] Notably, it has low surface tension which also leads to increased penetration and spreading. Debridement is not necessary for the action of efinaconazole.[29]

Pramiconazole

Pramiconazole is a newer triazole under development which has shown good *in-vitro* and clinical activity against dermatophytes, *Candida and Malassezia*. Both oral as well as topical preparations of pramiconazole have shown superior efficacy compared to itraconazole and terbinafine against *Microsporum canis* in guinea pigs.[31]

Other Newer 14α-lanosterol Demethylase Inhibitors

Novel 14α-lanosterol demethylase inhibitor arasertaconazole is under development and being studied in animal models[32] [Table 3].

2. Allylamines

Allylamines interfere with ergosterol synthesis similar to azoles but act at an earlier stage by inhibiting the formation of squalene epoxidase, which is a precursor of lanosterol and involved in the formation of cell membrane. Moreover, the inhibition of this pathway leads to the accumulation of high levels of squalene, which leads to increased membrane permeability and disruption of cellular organisation ensuring death of fungus. Terbinafine and naftifine are the two important drugs of this group.

Terbinafine

Efficacy of both oral and topical terbinafine (TBF) is well-documented in the management of dermatophytosis and has been widely used since the development of this drug. A recently conducted Cochrane review concluded the efficacy of terbinafine superior to placebo and almost similar to azoles. However, in many studies, terbinafine 1% cream has been used once daily and for a shorter duration.[12] It is FDA approved for the treatment of interdigital-type tinea pedis (athlete's foot), tinea cruris (jock itch), and tinea corporis (ringworm). Recently, a randomized control trial found similar efficacy and tolerability of 1% terbinafine cream to 1% eberconazole nitrate cream in the management of localized tinea corporis and cruris.[24] Similarly, another RCT found an efficacy of 1% terbinafine cream similar to 2% sertaconazole cream.[33] Various newer formulations, i.e., TBF-loaded liposome film, TBF-loaded liposome and ethosome, TBF-loaded transferosome, liposome poloxamer gel, microemulsion-based gel, and ethosome chitosan gel are in the developmental phase to increased penetration leading to augmented efficacy. Tanrıverdi *et al*. found the efficacy of liposome film formulation to be better compared to TBF-loaded liposome and ethosome, liposome poloxamer gel, and ethosome chitosan gel in the treatment of onychomycosis.[34]

Table 3: Investigational drugs under various phases of development[32,46,63-69]

Drug	Mechanism of Action	Concentration and vehicle	Phase of Clinical trial	Indications	Results of clinical trials	Spectrum of antimicrobial activity other than anti-dermatophytic
Arasertaconazole[32]	14α-lanosterol demethylase inhibitor	-	Animal model	-	Very potent *in vitro* activity against dermatophytes	Vulvovaginal Candidiasis Antifungal Antibacterial
BB2603[44]	Squalene epoxidase inhibition	Spray	Phase I/II	Onychomycosis and associated tinea pedis	Ongoing	-
ME1111[63]	Succinate dehydrogenase inhibition	0.06 to 32 mg/L	In vitro	-	Significant anti-dermatophytic action	
AR12 (OSU-03012)[64]	Acetyl-CoA synthetase inhibitor	5% (w/v)	Phase 1	Onychomycosis		1. Antifungal activity (Candida spp., Cryptococcus, Blastomyces, Histoplasma, and Coccidioides) 2. Antibacterial (Salmonella and Francisella) 3. Antiparasitic (Leishmania donovani) 4. Antiviral
SB208[65]	Cell death stimulants; Nitric oxide donors	2%, 4%, 12% gel once daily for 2 weeks	Phase 2	Interdigital tinea pedis	Statistically significant effect compared to vehicle	-
CD101 (Echinocandins)[66]	Glucan synthase inhibitors	Subcutaneous, 10-40 mg/kg/week, 2 doses	Animal model	Inoculum put over abraded area over back	Significant clinical and mycological efficacy compared to the vehicle	Systemic candidemia
NB-002[67]	Mechanically destabilize fungal hyphae	0.25%, and 0.5% Emulsion	Phase II	Distal subungual onychomycosis	Completed, no results available	Candida albicans Paecilomyces lilacinus, Fusarium spp., Scedosporium spp., and Scopulariopsis spp.
Hydroxychavicol[68]	Disruption of cell membrane integrity	-	*In vitro*	-	Significant anti-dermatophytic action	Candida parapsilosis
Phlorotannins[69]	1. Affect ergosterol composition of cell membrane 2. Affect the respiratory chain function	-	*In Vitro*	-	Significant anti-dermatophytic action	Candida species

Naftifine

Naftifine is a topical fungicidal allylamine that is effective against dermatophytes, *Candida and Aspergillus* species. It is also effective against Gram-negative and Gram-positive bacteria. Furthermore, naftifine has anti-inflammatory activity by targeting prostaglandin pathway.[35] Similar to terbinafine, it's efficacy is similar to azoles.[12] Recently, good efficacy of 2% naftifine gel has been documented in moccasin type tinea pedis in many RCTs.[36-38] A newer formulation, colloidal nanocarriers containing this drug, leads to increased penetration into the stratum corneum compared to the marketed formulation.[39] Once daily application of naftifine 2% cream and gel for 2 weeks is FDA approved for the treatment of interdigital tinea pedis, tinea cruris, and tinea corporis caused by the organism *T. rubrum* in adults over 18 years of age. Use of both the cream and gel formulations shows good rates of mycologic and clinical cure after 2–8 weeks of use.[35]

Butenafine

Butenafine is a benzylamine derivative which shows potent fungicidal activity particularly against dermatophytes, aspergillus, dimorphic, and dematiaceous fungi. In addition, it has anti-inflammatory activity.[40] Its mechanism of action

is similar to allylamines. Butenafine 1% cream is FDA approved for the treatment of interdigital tinea pedis, tinea cruris, and corporis. Various RCTs have found significantly superior efficacy of topical butenafine in the management of tinea compared to placebo whereas almost similar efficacy to those of topical azoles.[12,40] However, it may have the advantage of once daily application compared to azoles which decreases cost of therapy and increases compliance of therapy.[40] Recently, Thaker *et al*. in an RCT found topical 1% butenafine to be more efficacious, cost-effective, and equally safe compared to 2% sertaconazole for the treatment of tinea infections.[41] However, Thaker *et al*. in another RCT comparing Whitfield's ointment with weekly oral fluconazole (150 mg) to topical 1% butenafine in the treatment of tinea and found the former to be more efficacious, safe, and cost-effective.[42] A study from India found superior efficacy of butenafine 1% cream compared to terbinafine 1% cream for the treatment of tinea cruris.[43]

Novel Agents

A newer squalene epoxidase inhibitor BB2603 in a spray formulation is currently ongoing phase I/II trials for the treatment of onychomycosis and its associated tinea pedis[44] [Table 3].

3. Oxaboroles

Oxaboroles represent a new class of drug that acts primarily by blocking protein synthesis via the inhibition of leucylaminoacyl transfer RNA (t-RNA) synthetase.[45] Premature termination of protein synthesis leads to growth inhibition and death of the fungus. It has broad-spectrum antifungal activity including dermatophytes, such as *T. rubrum* and *T. mentagrophytes*, *C. albicans*, and nondermatophytic moulds.[19,45,46]

Tavaborole

Tavaborole, the first oxaborole, was approved by the FDA in July 2014 as a topical treatment of toenail onychomycosis caused by *T. rubrum* and *T. mentagrophytes*.[47] It has 1000 times greater selectivity for fungal aminoacyl transfer RNA synthetase (AARS) compared to mammalian AARS.[19] Tavaborole has a low-molecular-weight (152 kDa) leading to increased penetration through full-thickness human nail plates.[47] An *in-vitro* study on cadaveric nail demonstrated that 5% tavaborole solution has superior penetration capability compared to 8% ciclopirox solution after 14 days of daily application.[48] Once daily application is recommended for 48 weeks and it should be applied over the entire surface of the toenail and underneath the tip of the toenail.[19,48] Mycologic cure rate of tavaborole is lower than oral antifungal agents (30–36% vs 50–76%, respectively), however, it might provide an important alternative or adjuvant to available antifungal therapies.[48]

4. Hydroxypyridones

Hydroxypyridones are weak acids and show broad-spectrum antimicrobial activity. They act by chelating trivalent metal cations causing inhibition of metal-dependent enzymes leading to less degradation of cytoplasmic peroxides, increased sensitivity of cells to oxidative stress, and decreased levels of iron permeases or transporters. This unique and multilevel mechanism of action is responsible for very low incidence of resistance.[49] Ciclopirox is a prototype drug of this group. Rilopirox and octopirox (piroctone olamine) are other recently described drugs of this group. Various newer formulations, i.e., ciclopirox, dissolved in lipid diffusion enhancers, hydrosoluble preparations, formulation containing isopropyl alcohol, potassium hydroxide, and urea have led to excellent efficacy and permeation properties of ciclopirox while managing onychomycosis.[49-51] An RCT comparing P-3051 formulation (water-soluble ciclopirox 8% formulation in hydroxypropyl chitosan) to amorolfine 5% lacquer in the treatment of mild-to-moderate toenail onychomycosis found statistical superiority of P-3051 over amorolfine after 48 weeks in terms of treatment success while fungal eradication by P-3051 was statistically superior at week 24.[52]

5. Morpholines

Morpholines inhibit two enzymes, i.e., C-14 sterol reductase and C-8 sterol isomerase, in the ergosterol synthesis pathway. Amorolfine is the most commonly used drug of this group. It has been primarily used for the management of onychomycosis in lacquer formulation. Efficacy and safety of amorolfine cream have been found to be comparable to various azoles.[12,53]

6. Photodynamic therapy

Photodynamic therapy (PDT) involves the systemic or topical application of a photosensitizing agent followed by the selective illumination of the target lesion with light of an appropriate wavelength which leads to generation of free radicals and subsequent cell death. Aminolevulinic acid and methylene blue are the most commonly used photosensitizing agents for PDT. Various *in-vitro* as well as *in-vivo* studies have shown promising results.[54] In a recently conducted RCT, PDT using methylene blue as photosensitizing agent was found to have significantly superior efficacy over weekly 300 mg of oral fluconazole. PDT may offer a good prospect as alternative antifungal therapy in the current era of rapidly growing antifungal resistance.

8. Lasers

Many studies have investigated the efficacy of lasers for the management of onychomycosis. The exact mechanism of action of lasers in treating onychomycosis is not known but proposed mechanism includes heat disintegration of

fungal elements. Temperature exceeding 50°C leads to direct thermal killing. Various studies have used lasers with wavelengths varying from 780 to 3000 nm, but Nd: YAG 1064 nm laser is the most commonly used.[55] Although it provides an alternative treatment option with less procedural duration, current literature suggests limited success rate.[55,56]

New wine in old bottles: Older antifungal drugs in newer formulations

Due to widely increasing resistance, older drugs in newer formulations have also become the focus of attention. More recently, topical amphotericin B in lipid-based gel formulation has been found to effective in the treatment of various mucocutaneous fungal infections including dermatophytosis with a good safety profile.[57] Amphotericin B incorporated in microemulsion and nanoemulsion formulation shows an increased skin retention of the drug leading to better *in-vitro* antifungal activity.[1,58] Aqueous micellar solutions of econazole has 13-fold higher deposition of drug compared to conventional preparation.[59] Similarly, solid lipid nanoparticles and nanostructured lipid carriers have been found to increase occlusion, better penetration, less degradation of active drug, and sustained release over a longer duration leading to increased efficacy. These two drug delivery systems have been used for various drugs including clotrimazole, miconazole, ketoconazole, fluconazole, terbinafine, and griseofulvin, and are currently being considered among the most promising way of enhancing drug cutaneous penetration and efficacy for topical antifungal therapy. Transferosomes, also known as ultradeformable or flexible liposomes, have been used as carriers for griseofulvin and amphotericin B in the treatment of dermatophytosis with better efficacy.[59]

7. Future prospects

In-vitro studies have confirmed stronger *in-vitro* activity of echinocandins (anidulafungin, caspofungin, micafungin) against dermatophytes.[60-62] A recently developed novel antifungal drug, ME1111, fulfils the characteristics of an ideal antifungal drug for onychomycosis as it has potent antidermatophyte activity, low molecular weight leading to increased penetration, and maintaining good inhibitory activity even in the presence of keratin. It primarily acts by the inhibition of succinate dehydrogenase (complex II), a critical enzyme involved in electron transport chain in mitochondria.[63] AR12 (OSU-03012) is an acetyl CoA synthase inhibitor which is in phase 1 trials for malignancy but has also been found to have action on onychomycosis.[64] Other clinically relevant drugs have been briefly mentioned in Table 3.

Conclusion

The growing epidemic of recurrent/chronic dermatophytosis has led to the need for newer antifungal agents and/or preparations. Newer formulations or newer derivatives of existing drug classes and few newer drug classes have been described in the last 10 years, which provide hope to tackle this menace. Many newer agents are still undergoing experimental trials and require further study before they become commercially available. Newer topical agents, PDT, and lasers have all been tried, especially for onychomycosis which offers special challenges in successful management. Topical therapy has added advantage because of low risk of systemic side effects. It becomes difficult to choose one topical agent over the other given the efficacy is not much different between these. Similarly, all agents are quite safe for long-term use with no significant difference in the safety profile. However, long-term unsupervised use may lead to development of potential resistance. Many newer agents have an additional benefit of anti-inflammatory nature, thereby having relative preference over others, especially in inflamed and highly symptomatic lesions. Additional factors i.e., cost, easy availability, frequency, and ease of application may tilt the balance towards any one agent.

Judicious use of newer antifungals, emphasizing patient compliance, and prescribing without combining with oral/topical corticosteroids are all adjunctive steps necessary to offer cure to patients presenting with difficult to treat dermatophytosis.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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