Title
Antifungal agents for onychomycosis: new treatment strategies to improve safety

Journal
Dermatology Online Journal, 22(3)

Authors
Zane, Lee T
Chanda, Sanjay
Coronado, Dina
et al.

Publication Date
2016

DOI
10.5070/D3223030383

Volume 22 Number 3
March 2016

Review

Antifungal agents for onychomycosis: new treatment strategies to improve safety

Lee T Zane MD[1], Sanjay Chanda PhD[1], Dina Coronado[1], James Del Rosso DO FAOCD[2]

Dermatology Online Journal 22 (3): 1

[1]Anacor Pharmaceuticals, Inc., Palo Alto, CA; [2]Las Vegas Skin and Cancer Clinics/West Dermatology Group, Henderson, NV

Correspondence:

Lee T. Zane, MD
Anacor Pharmaceuticals, Inc.
1020 East Meadow Circle
Palo Alto, CA 94303-4230
Phone: (650) 543-7500
Fax: (650) 543-7662
Email: lzane@anacor.com

Abstract

Onychomycosis is a common and difficult-to-treat fungal infection of the nail unit that gradually leads to dystrophic changes of the nail plate and nail bed. If untreated, infection progresses and may lead to discomfort, reduced quality of life, and risk of complications in patients with comorbid conditions (eg, diabetes, human immunodeficiency virus, peripheral vascular disease). Onychomycosis treatments are designed to eradicate causative pathogens (most commonly *Trichophyton rubrum* and *Trichophyton mentagrophytes*), restore healthy nails, and prevent recurrence or spread of infection. Given the deep-seated nature of most cases of onychomycosis, an effective antifungal agent needs to achieve and maintain sufficient drug concentrations throughout the nail unit for the duration of healthy nail in-growth. Oral antifungal drugs are the most effective available therapy and are generally well tolerated, but may be limited by safety concerns and the potential for drug-drug interactions (DDIs). Thus, treating physicians and pharmacists must be cognizant of a patient's current medications; indeed, it may not be feasible to treat onychomycosis in patients with diabetes, heart disease, or depression because of the risk for DDIs. Current topical therapy is not associated with risk of DDIs. Tavaborole and efinaconazole, two recently approved topical agents, have demonstrated good nail penetration and high negative culture rates in clinical trials of patients with onychomycosis. This article provides the treating physician and pharmacist with information on the safety and effectiveness of current oral (allylamine, azole) and topical (ciclopirox, efinaconazole, tavaborole) treatment to aid in making informed treatment decisions based on the unique characteristics (medication history, comorbidities, nature of onychomycosis) of each patient.

Keywords: onychomycosis, antifungal agents, topical administration

Introduction

Onychomycosis is a common fungal infection of the nail unit that gradually leads to dystrophic changes of the nail plate and nail bed, including onycholysis, subungual debris, discoloration, and thickening. The most common type of onychomycosis is dermatophyte onychomycosis (tinea unguium) [1, 2]. The estimated incidence of onychomycosis is 8% to 14% based on surveys of adults seeking treatment at primary care or dermatology offices in the United States and Canada [1, 2]. The incidence of onychomycosis increases with age and may be as high as 50% among individuals older than 70 years [3]. Onychomycosis is reported to be more common among men than women and among those with diabetes and vascular disease [2]. In most patients,

onychomycosis affects one or more toenails and, in <5% of patients, it affects only the fingernails [1]. If fingernails are affected by dermatophytes onychomycosis, toenails (especially the large toenail) are almost always affected as well.

In the most common presentation of onychomycosis, the infection alters the nail unit, producing distal onycholysis, subungual hyperkeratosis, and thickening of the nail bed and nail plate (**Figure 1**) [3, 4]. If untreated, the infection progresses and may lead to discomfort related to pressure from a thickened and dystrophic toenail plate. In some cases, toenail onychomycosis may involve widespread damage to the nail plate and matrix, termination of nail plate growth or residual shortened nail owing to chronic trauma to the nail matrix, and ultimately detachment of the nail plate from the nail bed [3, 4]. When damage to the toenail becomes this extensive, patients may require prolonged, repeated courses of treatment in addition to intermittent debridement of the nail to achieve successful treatment outcomes [4].

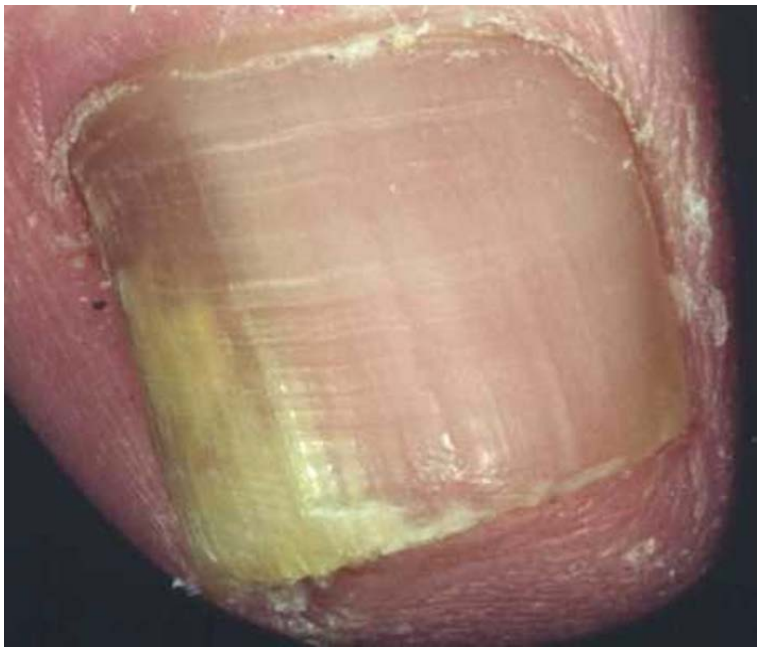


Figure 1. Image of patient with toenail onychomycosis

Onychomycosis may be associated with a greater risk of complications in patients with comorbid conditions including diabetes, human immunodeficiency virus, and peripheral vascular disease. Owing to the presence of peripheral neuropathy, patients with diabetes may not notice injuries to their toes caused by sharp edges of thick nails or downward pressure on the nail bed from the nail plate. Such injuries may serve as an entry point for pathogens and, in some cases, may result in serious complications including digital infections of soft tissues and/or bone (ie, osteomyelitis), foot ulceration, and limb amputation [3]. In addition, the physical appearance of the infected nail plate contributes to embarrassment and negative self-image and can adversely affect quality of life [5-7].

Onychomycosis is caused by a wide array of pathogens, most commonly the dermatophytes *Trichophyton rubrum* and *Trichophyton mentagrophytes*. However, up to 20% to 30% of cases are caused by non-dermatophyte fungi (molds) and yeasts including *Candida* species [1, 2, 8]. *Candida* onychomycosis is more common in fingernails than toenails [1]. Treatment of onychomycosis is designed to eradicate the causative pathogens, restore healthy nails, and prevent recurrence or spread of infection. Given the deep-seated nature of most cases of onychomycosis with involvement of the nail bed and nail plate, an effective antifungal agent needs to achieve and maintain sufficient drug concentrations throughout the complex nail unit during the duration of in-growth of a healthy nail [9].

Guidelines for the treatment of onychomycosis in the United States (US) were published by the American Academy of Dermatology in 1996 [10]. Guidelines from other western countries were published more than 5 years ago [11, 12]. Each of these guidelines recognizes oral and topical antifungal agents as therapeutic options for onychomycosis, although specific recommendations vary, and more recently developed agents are not included. Given the chronic nature of onychomycosis and the high incidence (which increases with age) among adults, successful disease management is critical and requires a complete understanding by health care providers and pharmacists of the treatment options available to affected patients. This commentary reviews the present day safety concerns associated with current oral and topical treatment approaches and discusses the potential for topical therapy to obviate potential side effects and drug interactions associated with oral (systemic) antifungal agents currently used to treat onychomycosis.

US Food and Drug Administration (FDA)–Approved Treatments for Onychomycosis

Oral Allylamine Antifungals

Oral antifungal agents are currently the most effective treatment options for onychomycosis, as they are delivered through systemic distribution into the nail bed, subsequently into the undersurface of the nail plate, and also into the nail plate at the point of juncture with the nail matrix [9]. Terbinafine (Lamisil®; Novartis Pharmaceuticals Corporation, East Hanover, NJ) is an oral allylamine antifungal drug that is currently approved by the US FDA for treatment of onychomycosis of the toenail or fingernail due to dermatophytes [13] (**Table 1**); it is the most frequently prescribed oral antifungal for onychomycosis in the US [14].

Terbinafine blocks fungal ergosterol biosynthesis through inhibition of squalene epoxidase, which results in the accumulation of squalene, increased permeability of the fungal cell membrane, and subsequent fungal cell death.

Table 1. Overview of US FDA-Approved Antifungal Agents for the Treatment of Toenail Onychomycosis

Antifungal Agent	Drug Class	Mechanism of Action	Indication	Recommended Dosage and Administration (Toenails)	Laboratory Monitoring and Other Requirements
Oral treatments					
Itraconazole [23]	Triazole antifungal	Inhibition of CYP450-dependent ergosterol synthesis	Treatment of onychomycosis of the toenail, with or without fingernail involvement, due to dermatophytes (tinea unguium)	• 200 mg once daily for 12 consecutive weeks • Capsules should be taken with full meal to ensure maximal absorption	• Liver function monitoring in patients with pre-existing hepatic function abnormalities
Terbinafine [13]	Allylamine antifungal	Inhibition of ergosterol biosynthesis via inhibition of squalene epoxidase	Treatment of onychomycosis of the toenail, with or without fingernail involvement, due to dermatophytes (tinea unguium)	• 250 mg once daily for 12 consecutive weeks	• Patients with known/suspected immunodeficiency should be monitored for complete blood counts • Measurement of liver enzymes is advised for all patients before initiating therapy
Topical treatments					
Ciclopirox [43]	Synthetic hydroxypyridone derivative	Chelation of polyvalent cations resulting inhibition of metal-dependent enzymes that degrade peroxides within fungal cell	Treatment of mild to moderate onychomycosis of fingernails and toenails without lunula involvement due to *T. rubrum*	• Once-daily application to all affected nails, evenly applied over entire nail plate • Avoid washing for 8 hours after application • If possible, medication should also be applied to hyponychium and under surface of the nail plate when it is free of the nail bed	• Unattached infected nail should be removed once a month • Filing of excess horny material should be done by trained professionals • Patients should file away loose nail material and trim nails as directed by their health care professional, or every 7 days after weekly removal of medication with alcohol

Efinaconazole [48]	Triazole antifungal	Inhibition of lanosterol 14α-demethylase in the ergosterol biosynthetic pathway	Treatment of onychomycosis of toenails due to *T. rubrum* and *T. mentagrophytes*	• Once-daily application for 48 weeks • Application should cover toenail, toenail folds, toenail bed, hyponychium, and the undersurface of toenail plate	• Not known whether nail polish or cosmetic nail products will affect how medication works
Tavaborole [53]	Boron-based antifungal	Blocks fungal protein synthesis via targeting of fungal cytoplasmic leucyl-tRNA synthetase, an aminoacyl-tRNA synthetase	Treatment of onychomycosis of toenails due to *T. rubrum* and *T. mentagrophytes*	• Once-daily application for 48 weeks • Application should cover entire toenail surface and under the tip of each toenail being treated	• Not known whether nail polish or cosmetic nail products will affect how medication works

US FDA, United States Food and Drug Administration

Treatment with oral terbinafine is associated with potential safety concerns. In 3 placebo-controlled clinical trials, commonly reported adverse events (incidence ≥1%) associated with treatment were hepatotoxicity, taste change or loss, and hematologic side effects. Taste disturbance associated with terbinafine can be severe, resulting in substantially reduced food intake, weight loss, anxiety, and depression; it may resolve weeks after discontinuing treatment, persist for over a year, or be permanent. Some patients may also experience similar change or loss in sense of smell during treatment [13].

Oral terbinafine is also associated with the risk of drug–drug interactions (DDIs) with drugs that share metabolism by the specific cytochrome P450 (CYP) enzymes that are inhibited by terbinafine [13]. Studies in human liver microsomes and clinical data demonstrate that terbinafine is a potent competitive inhibitor of CYP2D6 (**Table 2**) [13, 15, 16]. The inhibitor rate constant (K_i) of 0.03 μM is lower than the plasma and tissue drug concentrations typically achieved during oral treatment with terbinafine [15, 16]. This finding suggests that terbinafine can cause systemic accumulation of drugs that are predominantly metabolized by CYP2D6, including some beta-blockers, some antiarrhythmics, some tricyclic antidepressants, selective serotonin reuptake inhibitors (eg, fluoxetine, paroxetine), and certain opioids [16-22].

Table 2. Summary of Potential DDIs With Approved Oral and Topical Antifungal Agents

Antifungal Agent	Metabolism by CYP Enzymes	Inhibition/Induction of CYP Enzymes	Examples of Reported DDIs
Systemic therapies			
Itraconazole [23, 29-33, 36, 37, 39, 40]	CYP3A4	Potent inhibitor of CYP3A4	• Phenytoin • Digoxin, quinidine, dofetilide • Nifedipine, felodipine, nisoldipine, verapamil • Antacids, H_2-receptor antagonists, proton pump inhibitors • Corticosteroids • Pimozide • Cyclosporine • Atorvastatin, simvastatin, lovastatin

Terbinafine [15, 17-22]	• CYP2C9 • CYP1A2 • CYP3A4	Potent competitive inhibitor of CYP2D6	• Some beta blockers (ie, metoprolol) • Tricyclic antidepressants (eg, desipramine, imipramine, nortriptyline) • Some SSRIs (eg, paroxetine) • Codeine
Topical therapies			
Ciclopirox [46]	None (metabolism by glucuronidation)	None	None identified
Efinaconazole [51, 58]	Oxidation by CYP2C19 and CYP3A4	Inhibitor of CYP2C8, CYP2C9, CYP2C19, and CYP3A4	None identified
Tavaborole[a]	Oxidation by CYP3A5 and CYP2C18	Inhibitor of CYP2A6 and CYP2E1	None identified

CYP, cytochrome P450; DDIs, drug–drug interactions; SSRIs, selective serotonin reuptake inhibitors; TCAs, tricyclic antidepressants.
[a]Anacor Pharmaceuticals, Inc., Data on File, Studies 002-NCL PK-047-01 and 002-NCL PK-053-01.

The prescribing information for terbinafine includes a warning that terbinafine alters the metabolism of desipramine. Drug–drug interactions with cimetidine, fluconazole, cyclosporine, rifampin, and caffeine are also noted [13]; however, clinical relevance is not always apparent. The administration of terbinafine 250 mg orally for 21 days in combination with desipramine 50 mg to healthy volunteers resulted in a 2-fold increase in the maximum plasma concentration (C_{max}) and a 5-fold increase in exposure (area under the plasma concentration-time curve; AUC) to desipramine, with a corresponding decrease in the CYP2D6 metabolite, 2-hydroxydesimipramine [18]. Increased exposure to desipramine was still evident 4 weeks after discontinuation of terbinafine. The clinical relevance of this interaction is evidenced by reports of toxicity with similar tricyclic antidepressants when terbinafine is coadministered (ie, imipramine, nortriptyline, desipramine) [19, 20]. Terbinafine has also been shown to increase exposure to other CYP2D6 substrates including dextromethorphan and paroxetine [21, 22]. The potential for DDIs with terbinafine is an important consideration in patients receiving certain concomitant medications for other medical conditions.

Oral Azole Antifungals

The oral triazole antifungal itraconazole is also currently approved by the US FDA for the treatment of onychomycosis of the toenail due to dermatophytes [23]. The mechanism by which itraconazole blocks fungal ergosterol biosynthesis differs from that of terbinafine. Itraconazole inhibits CYP-dependent sterol 14α-demethylase, which causes depletion of ergosterol, accumulation of precursor sterols, impairments in fungal membrane structure and function, and fungal cell death [24]. The oral azole antifungal fluconazole, despite studies demonstrating efficacy, is not FDA-approved in the US for the treatment of onychomycosis, but is approved in Europe [25] and may be used by some physicians as an alternative systemic treatment option [26]. Also not approved by the US FDA, the oral azole ketoconazole was used in the past for treatment of onychomycosis, but use has recently declined because of low efficacy and safety concerns, including a significant risk of hepatotoxicity [27]. In fact, the US FDA has issued a strong warning that oral ketoconazole no longer be used for the treatment of superficial mycotic infections owing to hepatotoxicity risk [28].

As with oral allylamine antifungals, there is a risk of DDIs related to their mechanism of action, as lanosterol 14α-demethylase is a member of the CYP family [24]. In addition, itraconazole and its major sequential metabolites are metabolized by CYP3A4, and each functions as a potent CYP3A4 inhibitor (**Table 2**) [29]. As a result, itraconazole has the potential to interact with a wide range of drugs that are metabolized by CYP3A4 (primarily in the liver), including some 3-hydroxy-3-methyl-glutaryl CoA reductase inhibitors (ie, simvastatin, atorvastatin, lovastatin), some anticonvulsants (ie, phenytoin), pimozide, some benzodiazepines (ie, triazolam, midazolam), corticosteroids, cyclosporine, calcium channel blockers (ie, nifedipine, felodipine), as well as interaction with grapefruit juice, which inhibits CYP3A4 within the intestinal lining [23, 30, 31]. In healthy volunteers, administration of itraconazole 200 mg for 4 days resulted in 3- and 10-fold increases in exposure to single 40-mg doses of atorvastatin and simvastatin, respectively, reflecting the inhibition of CYP3A4-mediated metabolism [32, 33]. The clinical relevance of this DDI is illustrated by case reports of serious toxicity due to rhabdomyolysis soon after itraconazole was administered to patients who were receiving long-term statin therapy without previous difficulty [34, 35].

Clinical toxicity resulting from DDIs has occurred with the concurrent administration of itraconazole with the following drugs: midazolam and triazolam; calcium channel blockers such as nifedipine, nisoldipine, and verapamil; pimozide, quinidine and dofetilide; and some opiates such as methadone [23, 30, 36, 37]. Moreover, absorption of itraconazole may be substantially diminished if patients are ingesting other agents that reduce gastric acidity, including H_2-receptor antagonists, antacids, or proton pump inhibitors [23, 30, 37].

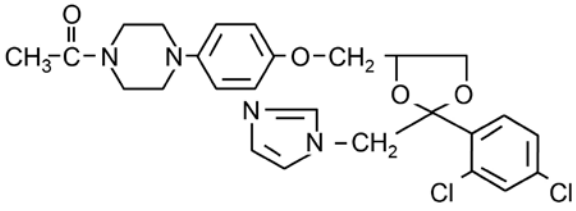
Itraconazole is also an inhibitor of P-glycoprotein (P-gp), a member of the adenosine triphosphate–binding cassette transporter superfamily located in cells of the gastrointestinal tract, kidneys, liver, and brain, which mediates drug efflux mechanisms in mammalian cells [38]. Notably, substrates for P-gp are similar to those for CYP3A4, and therefore it is often difficult to distinguish whether DDIs with itraconazole are mediated by inhibition of CYP3A4 or by inhibition of P-gp. Coadministration of itraconazole with digoxin has been associated with increased serum levels of digoxin with toxicity as the efflux of digoxin into the urine by renal tubular P-gp is inhibited by itraconazole. Studies in healthy volunteers show that itraconazole increases serum concentrations and reduces renal clearance of digoxin [39, 40]. Because digoxin is excreted mainly as unchanged drug in urine, this DDI may be caused by itraconazole inhibition of P-gp–mediated digoxin secretion in renal tubular cells.

The prescribing information for oral itraconazole includes a boxed warning describing the risks for congestive heart failure, cardiac effects, and drug interactions. The specific warning for drug interactions indicates that coadministration with cisapride, pimozide, quinidine, dofetilide, levacetylmethadol, and numerous other drugs is contraindicated, and that plasma concentrations of drugs metabolized by CYP3A4 are likely to be increased [23, 30]. Itraconazole has the potential to interact with a wide range of drugs that are metabolized by CYP3A4, including antiarrhythmic agents, antibiotics, antiepileptic agents, antihistamines, calcium antagonists, corticosteroids, immunosuppressive agents, sedatives/anxiolytics, and statins [30, 41]. In addition to the potential for DDIs, itraconazole is also associated with the possible risk of congestive heart failure and cardiac effects; thus, itraconazole should not be administered to individuals with ventricular dysfunction, including the presence or history of congestive heart failure [23, 30]. These potential risks are particularly challenging for elderly patients with onychomycosis, who often require multiple concomitant medications for comorbid conditions, notably diabetes and cardiovascular disorders. As previously noted, the incidence of onychomycosis increases with age and is highly prevalent in individuals >70 years of age [3]. A topical agent without CYP activity and low systemic absorption may often be preferable for this subset of patients, as they are more likely to be using multiple oral medications that could potentially interact, especially as CYP3A4 is the most common CYP450 enzyme involved in hepatic drug metabolism.

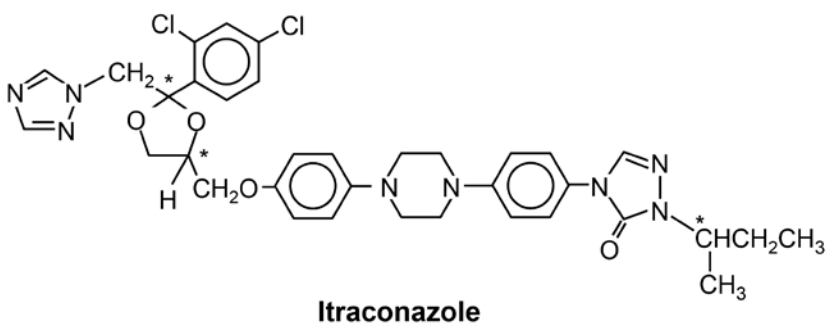
Ciclopirox 8% Nail Lacquer: A Topical Hydroxypyridone Derivative

Topical therapy is an important option for patients who choose to treat onychomycosis locally or who are unable to use an oral agent due to comorbid conditions and concomitant drug usage. However, to effectively eradicate the causative pathogen, the topical medication must penetrate the nail plate and reach the site of infection in the nail bed and matrix (when it is affected) at a sufficient concentration. The permeability of the nail plate is inherently low, and multiple factors affect drug permeation and uptake through the nail plate, including properties of the drug molecule (eg, size, polarity) and formulation (eg, vehicle, pH, drug concentration, presence of penetration enhancers), as well as properties of the nail itself (eg, thickness, hydration) [42]. The physical-chemical properties of terbinafine and itraconazole, including lipophilicity, high molecular weight, and limited water solubility do not allow penetration of the hydrophilic, dense keratin network of the nail plate, and thus render them unsuitable for topical application to the nail plate (**Figure 2**) [9].

Oral agents



Ketoconazole



Itraconazole

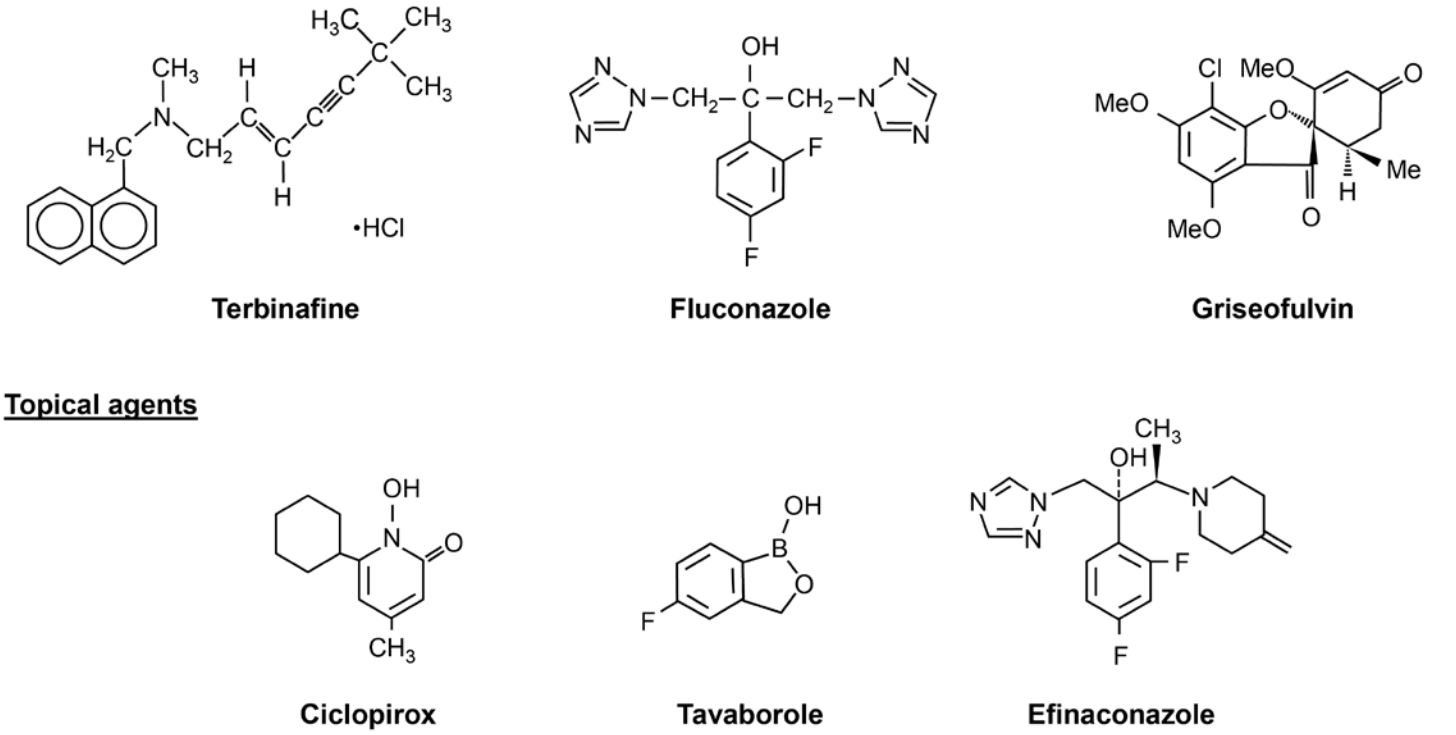


Figure 2. Chemical structures antifungal agents.

Ciclopirox 8% nail lacquer was the first topical antifungal agent approved by the FDA for the treatment of onychomycosis (**Table 1**) [43]. Ciclopirox is a synthetic hydroxypyridone derivative with broad-spectrum antifungal activity against dermatophytes and other pathogens involved in onychomycosis. Unlike the oral antifungal agents, ciclopirox does not affect sterol biosynthesis; rather, it is thought to chelate polyvalent cations in metal-dependent enzymes that are involved in fungal cell metabolism and growth [43-45].

Ciclopirox demonstrates antifungal activity in a time- and dose-dependent manner [46]; however, the overall nail penetration and systemic absorption of ciclopirox is very low because of its poor ability to penetrate the nail plate. Because the nail penetration and systemic absorption of ciclopirox are very low, the drug is unlikely to interact with drugs administered systemically (**Table 2**) [46]. No published studies have assessed the potential for ciclopirox to induce or inhibit CYP450 enzymes. In two randomized, controlled, multicenter trials, ciclopirox 8% applied as a lacquer once daily for 48 weeks for treatment of distal subungual onychomycosis was determined safe and effective; treatment-emergent adverse events (TEAEs) were transient and related to the application site **(Table 2)** [47].

Efinaconazole: A Topical Triazole Antifungal

Efinaconazole topical solution, 10% (Jublia®; Valeant Pharmaceuticals, Inc., Bridgewater, NJ) is a triazole antifungal agent approved by the FDA in June 2014 for the treatment of toenail onychomycosis caused by dermatophytes [48]. Efinaconazole exhibits broad-spectrum antifungal activity in vitro, with potency similar to or greater than that of drugs currently used in the treatment of onychomycosis [49]. Like other azole antifungal agents, efinaconazole inhibits lanosterol 14α-demethylase in the ergosterol biosynthetic pathway [50] and inhibits several CYP enzymes [51].

Plasma concentrations of efinaconazole and its major metabolite (H3) were determined after topical application of efinaconazole 10% solution to all 10 toenails once daily for 28 days in patients with severe onychomycosis [51]. Steady-state plasma concentrations were achieved by 14 days; the C_{max} of efinaconazole and the H3 metabolite on day 28 were low (0.67 and 2.36 ng/mL, respectively).

In human liver microsomes, efinaconazole inhibited CYP2C8, CYP2C9, CYP2C19, and CYP3A4 (K_i = <700 ng/mL), and the H3 metabolite inhibited CYP2B6 (K_i = 4840 ng/mL) [51]. The strongest inhibition with efinaconazole was observed against CYP2C9 (K_i = 91 ng/mL). The K_i values for CYP inhibition by efinaconazole and the H3 metabolite are well above the respective C_{max}

values observed at steady state in patients with onychomycosis, suggesting a low potential for DDIs with concomitantly administered drugs. However, no additional studies have assessed inhibition or induction of CYP enzymes with efinaconazole.

Two identical phase 3 studies assessed the safety and efficacy of efinaconazole applied once daily for 48 weeks in patients 18 to 70 years of age with mild to moderate distal lateral subungual onychomycosis involving up to 50% of the target toenail [52]. In both studies, patients were randomly assigned (3:1) to receive efinaconazole or vehicle; nail debridement was not performed. Rates of adverse events with efinaconazole, including instances of local application site reactions, were generally similar to those with vehicle. Most adverse events were generally mild or moderate in severity and not related to treatment; the most common adverse event resulting in study discontinuation was application site reactions. Complete cure rates, the primary efficacy endpoint in both studies, were significantly greater for efinaconazole compared with placebo (17.8% vs. 3.3% and 15.2% vs. 5.5%, respectively, for the two studies; $P<0.001$ for both) [52].

Tavaborole: A Novel, Boron-Based Pharmaceutical Antifungal

Tavaborole topical solution, 5% (Kerydin®; Anacor Pharmaceuticals, Inc, Palo Alto, CA), is a novel, boron-based pharmaceutical agent approved by the FDA in July 2014 for the treatment of onychomycosis of the toenails due to T. rubrum or T. mentagrophytes [53]. Tavaborole is a low-molecular-weight (152 kDa) and highly specific fungal protein synthesis inhibitor that forms a boron-based bond at the enzyme-editing site to prevent catalytic turnover of leucyl-tRNA synthetase and block fungal protein synthesis [54]. Tavaborole exhibits broad-spectrum antifungal activity in vitro against dermatophytes and other fungi recovered from subungual specimens [55, 56]. The low molecular weight of tavaborole allows a high amount of penetration through full-thickness human nail plates [55].

The systemic absorption of tavaborole was investigated in a phase 1 trial involving 24 patients with distal subungual onychomycosis in at least four toenails, of which at least one was a great toenail (Anacor Pharmaceuticals, Inc., Data on File, Study 002-CLN PK-003-01). Steady-state plasma concentrations were achieved within 11 days after once-daily topical application of a 5% solution to all 10 toenails and the 2 mm of skin surrounding the toenails. The value for observed C_{max} after 18 days of daily application was low (5.2 ng/mL). Because of the small size and polarity of tavaborole, it is likely that it is quickly metabolized.

In vitro studies were conducted to evaluate the potential of tavaborole to induce or inhibit CYP enzymes. Tavaborole at concentrations up to 12.6 μM (1.9 μg/mL) caused no meaningful change (on average, <15% increase or decrease) in the activities of CYP1A2, CYP3A4/5, CYP2B6, CYP2C8, CYP2C9, and CYP2C19 in cultured human hepatocytes.

The ability of tavaborole to inhibit CYP subtypes was evaluated in human liver microsomes at concentrations ranging from 0.1 to 100 μM (15.2 ng/mL to 15.2 μg/mL) (Anacor Pharmaceuticals, Inc., Data on File, Study 002-NCL PK-053-01). At these concentrations, tavaborole did not cause direct or time-dependent inhibition of CYP1A2, CYP3A4/5, CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP2D6. In addition, tavaborole showed some evidence of time-dependent and partial NADPH-dependent inhibition of CYP2A6 activity at a concentration >30 μM (**Table 2**).

The CYP subtypes responsible for tavaborole metabolism were identified using human liver microsomes (Supersomes™, BD Biosciences, San Jose, CA). Oxidation of tavaborole was primarily mediated by CYP3A5 and CYP2C18, whereas CYP2C19 and CYP3A4 played minor roles (Anacor Pharmaceuticals, Inc., Data on File, Study 002-NCL PK-047-01).

Two phase 3 clinical trials of identical design evaluated the safety and efficacy of tavaborole compared with vehicle in adults 18 to 80 years of age with distal subungual toenail onychomycosis involving up to 60% of the great toenail [57]. Patients were randomly assigned (2:1) to receive tavaborole or vehicle; nail debridement was not performed. Rates of adverse events reported with tavaborole were low, and treatment-related adverse events were localized to the application site; the most common were exfoliation, dermatitis, and erythema (1.3%–2.7%). Tavaborole was significantly more effective in producing complete cure, treatment success, and negative mycology compared with vehicle. Respective rates of complete cure with tavaborole vs. vehicle at week 52 were 6.5% vs. 0.5% in study 1 and 9.1% vs. 1.5% in study 2 ($P\leq0.001$ for both comparisons). Negative culture rates with tavaborole vs. vehicle were 87.0% vs. 47.9% and 85.4% vs. 51.2% in studies 1 and 2, respectively. Mycological cure rates of the target great toenail with tavaborole vs. vehicle were 31.1% vs. 7.2% and 35.9% vs. 12.2% in studies 1 and 2, respectively.

Conclusion

Onychomycosis is a difficult-to-treat infection, and becomes more challenging in elderly patients and those with comorbid conditions who require multiple concomitant medications. Oral antifungal drugs are the most effective available therapy and are generally well tolerated, but may be limited by safety concerns. The potential risk of DDIs with concomitant medications could

have substantial implications for the treating physician and pharmacist. Managing the treatment of these patients requires a thorough review and understanding of a patient's current medications and how they are metabolized. The risk of adjusting, substituting, or stopping other medications in order to accommodate oral antifungal therapy is a complex challenge. In many cases, it may not be feasible to treat onychomycosis in patients with diabetes, heart disease, or depression because of the risk for DDIs in these patients requiring therapies that cannot be easily discontinued or substantially altered.

Currently available topical antifungal therapy is not associated with risk of DDIs or systemic toxicity. However, topical medications must penetrate the nail plate at sufficient concentrations to eradicate the infection and multiple factors can affect drug penetration (eg, nail permeability, size and ionic charge of the molecule, drug formulation) [42]. Tavaborole and efinaconazole, two new topical agents recently approved by the FDA, both demonstrate good nail penetration and achieve high rates of negative cultures in treated patients [57]. With once-daily application over 48 weeks, systemic exposure is negligible, and the possibility for DDIs is low.

Sources of Support/Disclosures

Writing and editorial assistance was provided by Callie Grimes, PhD, of Peloton Advantage, LLC, Parsippany, NJ, and was supported by Anacor Pharmaceuticals, Inc., Palo Alto, CA. Diane Nelson, RN, MPH of Anacor Pharmaceuticals, Inc. provided critical review and revision to the manuscript. The authors were fully responsible for the content, editorial decisions, and opinions expressed in the current article. No author received an honorarium related to the development of this manuscript.

Lee Zane, Sanjay Chanda, and Dina Coronado are employees and stock shareholders of Anacor Pharmaceuticals, Inc. James Del Rosso is a consultant and speaker for the following companies that have existing products, commercial interest, and/or research interest in fungal infections including onychomycosis: Anacor Pharmaceuticals, Inc., Aqua Pharmaceuticals, Merz Pharmaceuticals, and Valeant Pharmaceuticals.

References

1. Gupta AK, Jain HC, Lynde CW, Macdonald P, Cooper EA, Summerbell RC. Prevalence and epidemiology of onychomycosis in patients visiting physicians' offices: a multicenter canadian survey of 15,000 patients. J Am Acad Dermatol. 2000 Aug;43(2 Pt 1):244-8. [PMID: 10906646]
2. Ghannoum MA, Hajjeh RA, Scher R, Konnikov N, Gupta AK, Summerbell R, Sullivan S, Daniel R, Krusinski P, Fleckman P, Rich P, Odom R, Aly R, Pariser D, Zaiac M, Rebell G, Lesher J, Gerlach B, Ponce-De-Leon GF, Ghannoum A, Warner J, Isham N, Elewski B. A large-scale North American study of fungal isolates from nails: the frequency of onychomycosis, fungal distribution, and antifungal susceptibility patterns. J Am Acad Dermatol. 2000 Oct;43(4):641-8. [PMID: 11004620]
3. Thomas J, Jacobson GA, Narkowicz CK, Peterson GM, Burnet H, Sharpe C. Toenail onychomycosis: an important global disease burden. J Clin Pharm Ther. 2010 Oct;35(5):497-519. [PMID: 20831675]
4. Del Rosso JQ. The role of topical antifungal therapy for onychomycosis and the emergence of newer agents. J Clin Aesthet Dermatol. 2014 Jul;7(7):10-8. [PMID: 25053979]
5. Elewski BE. The effect of toenail onychomycosis on patient quality of life. Int J Dermatol. 1997 Oct;36(10):754-6. [PMID: 9372349]
6. Drake LA, Scher RK, Smith EB, Faich GA, Smith SL, Hong JJ, Stiller MJ. Effect of onychomycosis on quality of life. J Am Acad Dermatol. 1998 May;38(5 Pt 1):702-4. [PMID: 9591814]
7. Drake LA, Patrick DL, Fleckman P, Andr J, Baran R, Haneke E, Sapede C, Tosti A. The impact of onychomycosis on quality of life: development of an international onychomycosis-specific questionnaire to measure patient quality of life. J Am Acad Dermatol. 1999 Aug;41(2 Pt 1):189-96. [PMID: 10426887]
8. Foster KW, Ghannoum MA, Elewski BE. Epidemiologic surveillance of cutaneous fungal infection in the United States from 1999 to 2002. J Am Acad Dermatol. 2004 May;50(5):748-52. [PMID: 15097959]
9. Alley MR, Baker SJ, Beutner KR, Plattner J. Recent progress on the topical therapy of onychomycosis. Expert Opin Investig Drugs. 2007 Feb;16(2):157-67. [PMID: 17243936]
10. Guidelines of care for superficial mycotic infections of the skin: onychomycosis. Guidelines/Outcomes Committee. American Academy of Dermatology. J Am Acad Dermatol. 1996 Jan;34(1):116-21. [PMID: 8543680]
11. Roberts DT, Taylor WD, Boyle J. Guidelines for treatment of onychomycosis. Br J Dermatol. 2003 Mar;148(3):402-10. [PMID: 12653730]
12. Seebacher C, Brasch J, Abeck D, Cornely O, Effendy I, Ginter-Hanselmayer G, Haake N, Hamm G, Hipler UC, Hof H, Korting HC, Mayser P, Ruhnke M, Schlacke KH, Tietz HJ. Onychomycosis. Mycoses. 2007 Jul;50(4):321-7. [PMID: 17576328]
13. Lamisil [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2013.

14. Gupta AK, Ryder JE, Lynch LE, Tavakkol A. The use of terbinafine in the treatment of onychomycosis in adults and special populations: a review of the evidence. J Drugs Dermatol. 2005 May;4(3):302-8. [PMID: 15898285]
15. Vickers AE, Sinclair JR, Zollinger M, Heitz F, Glanzel U, Johanson L, Fischer V. Multiple cytochrome P-450s involved in the metabolism of terbinafine suggest a limited potential for drug-drug interactions. Drug Metab Dispos. 1999 Sep;27(9):1029-38. [PMID: 10460803]
16. Abdel-Rahman SM, Marcucci K, Boge T, Gotschall RR, Kearns GL, Leeder JS. Potent inhibition of cytochrome P-450 2D6-mediated dextromethorphan O-demethylation by terbinafine. Drug Metab Dispos. 1999 Jul;27(7):770-5. [PMID: 10383919]
17. Ingelman-Sundberg M. Genetic polymorphisms of cytochrome P450 2D6 (CYP2D6): clinical consequences, evolutionary aspects and functional diversity. Pharmacogenomics J. 2005;5(1):6-13. [PMID: 15492763]
18. Madani S, Barilla D, Cramer J, Wang Y, Paul C. Effect of terbinafine on the pharmacokinetics and pharmacodynamics of desipramine in healthy volunteers identified as cytochrome P450 2D6 (CYP2D6) extensive metabolizers. J Clin Pharmacol. 2002 Nov;42(11):1211-8. [PMID: 12412819]
19. Teitelbaum ML, Pearson VE. Imipramine toxicity and terbinafine. Am J Psychiatry. 2001 Dec;158(12):2086. [PMID: 11729036]
20. O'Reardon JP, Hetznecker JM, Rynn MA, Baldassano CF, Szuba MP. Desipramine toxicity with terbinafine. Am J Psychiatry. 2002 Mar;159(3):492. [PMID: 11870022]
21. Abdel-Rahman SM, Gotschall RR, Kauffman RE, Leeder JS, Kearns GL. Investigation of terbinafine as a CYP2D6 inhibitor in vivo. Clin Pharmacol Ther. 1999 May;65(5):465-72. [PMID: 10340911]
22. Yasui-Furukori N, Saito M, Inoue Y, Niioka T, Sato Y, Tsuchimine S, Kaneko S. Terbinafine increases the plasma concentration of paroxetine after a single oral administration of paroxetine in healthy subjects. Eur J Clin Pharmacol. 2007 Jan;63(1):51-6. [PMID: 17124578]
23. Omnel [package insert]. Greensboro, NC: Merz Pharmaceuticals, LLC; 2012.
24. Ghannoum MA, Rice LB. Antifungal agents: mode of action, mechanisms of resistance, and correlation of these mechanisms with bacterial resistance. Clin Microbiol Rev. 1999 Oct;12(4):501-17. [PMID: 10515900]
25. Questions and answers on diflucan and associated names (fluconazole, 50, 100, 150 and 200 mg capsules, oral solution 5 mg/ml, powder for oral suspension 10 mg/ml or 40 mg/ml, solution for infusion 2 mg/ml). Accessed at http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/Diflucan_30/WC500108008.pdf on 17 November 2015.
26. Elewski B, Pollak R, Ashton S, Rich P, Schlessinger J, Tavakkol A. A randomized, placebo- and active-controlled, parallel-group, multicentre, investigator-blinded study of four treatment regimens of posaconazole in adults with toenail onychomycosis. Br J Dermatol. 2012 Feb;166(2):389-98. [PMID: 21967490]
27. Elewski B, Tavakkol A. Safety and tolerability of oral antifungal agents in the treatment of fungal nail disease: a proven reality. Ther Clin Risk Manag. 2005 Dec;1(4):299-306. [PMID: 18360572]
28. FDA drug safety communication: FDA limits usage of Nizoral (ketoconazole) oral tablets due to potentially fatal liver injury and risk of drug interactions and adrenal gland problems. Accessed at http://www.fda.gov/downloads/Drugs/DrugSafety/UCM362444.pdf on 17 November 2015.
29. Isoherranen N, Kunze KL, Allen KE, Nelson WL, Thummel KE. Role of itraconazole metabolites in CYP3A4 inhibition. Drug Metab Dispos. 2004 Oct;32(10):1121-31. [PMID: 15242978]
30. Bruggemann RJ, Alffenaar JW, Blijlevens NM, Billaud EM, Kosterink JG, Verweij PE, Burger DM. Clinical relevance of the pharmacokinetic interactions of azole antifungal drugs with other coadministered agents. Clin Infect Dis. 2009 May;48(10):1441-58. [PMID: 19361301]
31. Yu DT, Peterson JF, Seger DL, Gerth WC, Bates DW. Frequency of potential azole drug-drug interactions and consequences of potential fluconazole drug interactions. Pharmacoepidemiol Drug Saf. 2005 Nov;14(11):755-67. [PMID: 15654717]
32. Neuvonen PJ, Kantola T, Kivisto KT. Simvastatin but not pravastatin is very susceptible to interaction with the CYP3A4 inhibitor itraconazole. Clin Pharmacol Ther. 1998 Mar;63(3):332-41. [PMID: 9542477]
33. Kantola T, Kivisto KT, Neuvonen PJ. Effect of itraconazole on the pharmacokinetics of atorvastatin. Clin Pharmacol Ther. 1998 Jul;64(1):58-65. [PMID: 9695720]
34. Lees RS, Lees AM. Rhabdomyolysis from the coadministration of lovastatin and the antifungal agent itraconazole. N Engl J Med. 1995 Sep;333(10):664-5. [PMID: 7637734]
35. Horn M. Coadministration of itraconazole with hypolipidemic agents may induce rhabdomyolysis in healthy individuals. Arch Dermatol. 1996 Oct;132(10):1254. [PMID: 8859048]
36. Sporanox capsules [package insert]. Titusville, NJ: Janssen Pharmaceuticals, Inc; 2012.
37. Sporanox capsules [product information]. Macquarie Park, Australia: Janssen-Cilag Pty Ltd; 2013.
38. Wang EJ, Lew K, Casciano CN, Clement RP, Johnson WW. Interaction of common azole antifungals with P glycoprotein. Antimicrob Agents Chemother. 2002 Jan;46(1):160-5. [PMID: 11751127]
39. Partanen J, Jalava KM, Neuvonen PJ. Itraconazole increases serum digoxin concentration. Pharmacol Toxicol. 1996 Nov;79(5):274-6. [PMID: 8936563]
40. Jalava KM, Partanen J, Neuvonen PJ. Itraconazole decreases renal clearance of digoxin. Ther Drug Monit. 1997 Dec;19(6):609-13. [PMID: 9421099]

41. Venkatakrishnan K, von Moltke LL, Greenblatt DJ. Effects of the antifungal agents on oxidative drug metabolism: clinical relevance. Clin Pharmacokinet. 2000 Feb;38(2):111-80. [PMID: 10709776]
42. Murdan S. Drug delivery to the nail following topical application. Int J Pharm. 2002 Apr;236(1-2):1-26. [PMID: 11891066]
43. Penlac [package insert]. Bridgewater, NJ: Dermik Laboratories, a division of sanofi-aventis U.S. LLC; 2006.
44. Leem SH, Park JE, Kim IS, Chae JY, Sugino A, Sunwoo Y. The possible mechanism of action of ciclopirox olamine in the yeast *Saccharomyces cerevisiae*. Mol Cells. 2003 Feb;15(1):55-61. [PMID: 12661761]
45. Sigle HC, Thewes S, Niewerth M, Korting HC, Schafer-Korting M, Hube B. Oxygen accessibility and iron levels are critical factors for the antifungal action of ciclopirox against *Candida albicans*. J Antimicrob Chemother. 2005 May;55(5):663-73. [PMID: 15790671]
46. Bohn M, Kraemer KT. Dermatopharmacology of ciclopirox nail lacquer topical solution 8% in the treatment of onychomycosis. J Am Acad Dermatol. 2000 Oct;43(4 Suppl):S57-S69. [PMID: 11051135]
47. Gupta AK, Fleckman P, Baran R. Ciclopirox nail lacquer topical solution 8% in the treatment of toenail onychomycosis. J Am Acad Dermatol. 2000 Oct;43(4 Suppl):S70-S80. [PMID: 11051136]
48. Jublia [package insert]. Bridgewater, NJ: Valeant Pharmaceuticals North America, LLC; 2015.
49. Jo Siu WJ, Tatsumi Y, Senda H, Pillai R, Nakamura T, Sone D, Fothergill A. Comparison of in vitro antifungal activities of efinaconazole and currently available antifungal agents against a variety of pathogenic fungi associated with onychomycosis. Antimicrob Agents Chemother. 2013 Apr;57(4):1610-6. [PMID: 23318803]
50. Tatsumi Y, Nagashima M, Shibanushi T, Iwata A, Kangawa Y, Inui F, Siu WJ, Pillai R, Nishiyama Y. Mechanism of action of efinaconazole, a novel triazole antifungal agent. Antimicrob Agents Chemother. 2013 May;57(5):2405-9. [PMID: 23459486]
51. Jarratt M, Siu WJ, Yamakawa E, Kodera N, Pillai R, Smith K. Safety and pharmacokinetics of efinaconazole 10% solution in healthy volunteers and patients with severe onychomycosis. J Drugs Dermatol. 2013 Sep;12(9):1010-6. [PMID: 24002148]
52. Elewski BE, Rich P, Pollak R, Pariser DM, Watanabe S, Senda H, Ieda C, Smith K, Pillai R, Ramakrishna T, Olin JT. Efinaconazole 10% solution in the treatment of toenail onychomycosis: Two phase III multicenter, randomized, double-blind studies. J Am Acad Dermatol. 2013 Apr;68(4):600-8. [PMID: 23177180]
53. Kerydin [package insert]. Palo Alto, CA: Anacor Pharmaceuticals, Inc.; 2015.
54. Rock FL, Mao W, Yaremchuk A, Tukalo M, Crepin T, Zhou H, Zhang YK, Hernandez V, Akama T, Baker SJ, Plattner JJ, Shapiro L, Martinis SA, Benkovic SJ, Cusack S, Alley MR. An antifungal agent inhibits an aminoacyl-tRNA synthetase by trapping tRNA in the editing site. Science. 2007 Jun;316(5832):1759-61. [PMID: 17588934]
55. Barak O, Loo DS. AN-2690, a novel antifungal for the topical treatment of onychomycosis. Curr Opin Investig Drugs. 2007 Aug;8(8):662-8. [PMID: 17668368]
56. Hold KM, Sanders V, Bu W, Baker SJ, Plattner JJ, Maples KR, Wheeler C, Jones T, Beutner K. Nail penetration and nail concentration of AN2690, a novel broad-spectrum antifungal agent in development for the topical treatment of onychomycosis [poster]. Presented at: Annual Meeting of the American Association of Pharmaceutical Scientists. October 29-November 2, 2006; San Antonio, TX.
57. Elewski BE, Rich P, Wiltz H, Aly R, Baldwin SL, Zane LT, Gonzalez Soto R. Effectiveness and safety of tavaborole, a novel boron-based molecule for the treatment of onychomycosis: results from two phase 3 studies [poster]. Presented at: Women's and Pediatric Dermatology Seminar. October 4-6, 2013; Newport Beach, CA.
58. Chiang G. Clinical review resubmission: efinaconazole. Accessed at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/203567Orig1s000MedR.pdf on 16 November 2015.