Topical Antifungals for Onychomycosis: In Vitro Antifungal Activity, Ex Vivo Nail Penetration, and Clinical Efficacy

Ali Elabbasi[1]; Ahmed Kadry[1]; Warren S. Joseph, DPM[2]; Boni Elewski, MD[3]; Shari Lipner, MD, PhD[4]; Eric Guenin, PharmD, PhD, MPH[5]; Mahmoud Ghannoum, PhD[1,6]

[1]Case Western Reserve University, Cleveland, OH; [2]Arizona College of Podiatric Medicine, Midwestern University, Glendale, AZ; [3]University of Alabama at Birmingham School of Medicine, Birmingham, AL; [4]Weill Cornell Medicine, New York, NY; [5]Ortho Dermatologics,* Bridgewater, NJ; [6]University Hospitals Cleveland Medical Center, Cleveland, OH

Ortho Dermatologics is a division of Bausch Health US, LLC

SYNOPSIS

- Topical antifungals for toenail onychomycosis may be preferred over oral antifungals for patients for whom systemic adverse events, drug-drug interactions, or contraindications associated with oral antifungals are of concern[1]
- Three topical antifungals have been approved by the US Food and Drug Administration (FDA) for the treatment of toenail onychomycosis: ciclopirox 8% lacquer, efinaconazole 10% solution, and tavaborole 5% solution[2-4]
- To achieve clinical efficacy, topicals must penetrate the nail and deliver an inhibitory concentration of free drug to the site of infection[5]

OBJECTIVES

- The objective of this narrative review is to compare in vitro antifungal activity, ex vivo human nail penetration, and clinical efficacy of the 3 topicals approved for toenail onychomycosis (**Table 1**)

TABLE 1. **FDA-Approved Topical Antifungals for Onychomycosis**

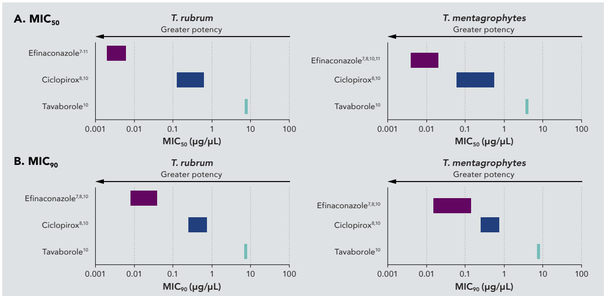
	Efinaconazole 10%[2]	Ciclopirox 8%[3]	Tavaborole 5%[4]
First approval	2014	1999	2014
Dosing	Once daily for 48 weeks	Once daily for 48 weeks + frequent nail debridement	Once daily for 48 weeks
Indication	Onychomycosis of the toenail(s) due to *Trichophyton rubrum* and *T. mentagrophytes*	Immunocompetent patients with mild to moderate onychomycosis of fingernails and toenails without lunula involvement due to *T. rubrum*	Onychomycosis of the toenails due to *T. rubrum* and *T. mentagrophytes*
Proposed MOA	Inhibits biosynthesis of ergosterol via inhibition of fungal lanosterol 14α-demethylase (a cytochrome P450–dependent enzyme)	Inhibits metal-dependent enzymes responsible for degradation of fungal cell peroxides via polyvalent cation chelation	Inhibits protein synthesis via inhibition of an aminoacyl-transfer ribonucleic acid synthetase

[a]Ergosterol is a vital component of fungal cell membranes.
FDA, US Food and Drug Administration.

IN VITRO ANTIFUNGAL ACTIVITY

- In vitro antifungal activity was defined as the minimum inhibitory concentration of drug needed to inhibit 50% (MIC_{50}) or 90% (MIC_{90}) growth of *Trichophyton rubrum* and *T. mentagrophytes*, the 2 most common dermatophyte causes of toenail onychomycosis[6]
  - Lower MICs indicate greater antifungal activity
  - MIC data were collected from papers published since 2010 in which MIC_{50} and/or MIC_{90} data were reported for any of the 3 antifungals[7-11]
- Against both *Trichophyton* species, MIC_{50} was lower for efinaconazole than for ciclopirox or tavaborole, indicating greater antifungal potency (**Figure 1A**)
- Using the more stringent MIC_{90}, antifungal potency was also greater for efinaconazole than for ciclopirox or tavaborole (**Figure 1B**)

FIGURE 1. **In Vitro Antifungal Activity Against *T. rubrum* and *T. mentagrophytes***

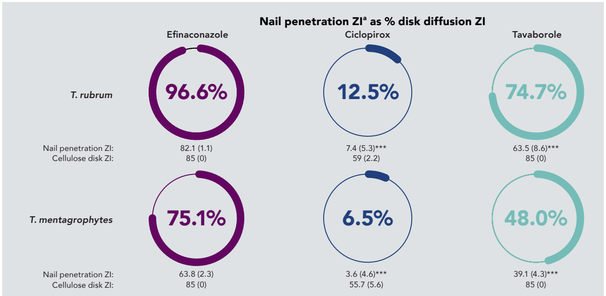


MIC_{50}, minimum inhibitory concentration of drug needed to inhibit 50% growth; MIC_{90}, minimum inhibitory concentration of drug needed to inhibit 90% of growth.

EX VIVO HUMAN NAIL PENETRATION[5]

- To assess antifungal activity via nail penetration, each antifungal was applied to a human cadaverous toenail; disks punched from coated nails were placed treated side up onto agar plates seeded with clinical isolates of each fungal species
- To assess intrinsic antifungal activity (positive control), each drug was applied to keratin-free cellulose disks and placed directly onto seeded agar plates
- For both assessments, antifungal activity was measured as the radius of the area of no fungal growth after incubation (zone of inhibition [ZI])
- Nail penetration efficiency was defined as the nail penetration ZI as a percentage of the disk diffusion ZI
- Nail penetration ZIs against both *Trichophyton* species were significantly larger for efinaconazole than for ciclopirox or tavaborole (all $P<0.001$; **Figure 2**)
- Against both species, nail penetration efficiency with efinaconazole > tavaborole >> ciclopirox (**Figure 2**)

FIGURE 2. **Efficiency of Penetration Through Human Cadaverous Toenail**

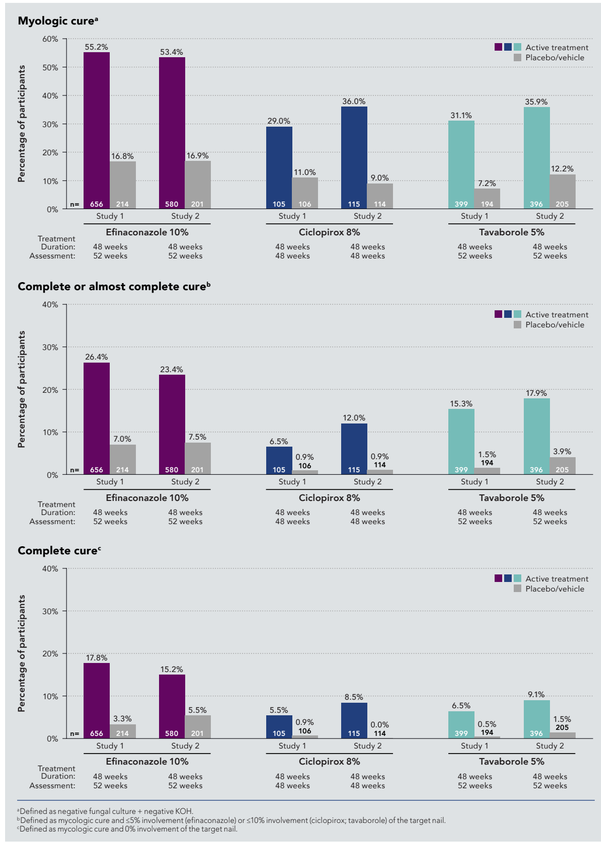


***P<0.001 vs efinaconazole.
[a]ZI was defined as the radius of the area of no fungal growth, disregarding any feathering. ZIs are presented as mean (SD), mm. Maximum ZI was 85 mm.
ZI, zone of inhibition.

CLINICAL EFFICACY AND SAFETY

- Clinical efficacy data were gathered from prescribing information and/or publications of pivotal phase 3 clinical trials, in which each drug was applied daily for 48 weeks (plus debridement with ciclopirox)[3,4,12]
- Rates of mycological cure, complete/almost complete cure, and complete cure were greater with efinaconazole 10% solution than ciclopirox 8% lacquer or tavaborole 5% solution after 48 weeks of once-daily treatment (**Figure 3**)
- Rates of treatment-related adverse effects were similar across the 3 topicals; the most common included nail disorders (eg, ingrown nail) and application site dermatitis and erythema[3,4,12,13]

FIGURE 3. **Clinical Efficacy**



[a]Defined as negative fungal culture + negative KOH.
[b]Defined as mycologic cure and ≤5% involvement (efinaconazole) or ≤10% involvement (ciclopirox; tavaborole) of the target nail.
[c]Defined as mycologic cure and 0% involvement of the target nail.

CONCLUSIONS

- Efficacy of topical treatments for onychomycosis requires potent antifungal activity and the ability to penetrate through the keratin-rich nail to reach the infection site
- Of the 3 FDA-approved topicals, efinaconazole demonstrated greater antifungal potency and inhibition of fungal growth after application to human nails
  - This may be due to the lower keratin affinity/higher release of efinaconazole (vs ciclopirox)[14,15] and greater antifungal activity of efinaconazole in the presence of keratin (vs ciclopirox and tavaborole)
- The improved in vitro and ex vivo activity of efinaconazole is supported by clinical trial data, in which rates of complete cure with efinaconazole 10% solution were 2- to 3-fold higher than with ciclopirox 8% lacquer or tavaborole 5% solution, with mycologic cure rates within the range of some oral antifungals[16]

REFERENCES

1. Lipner SR, et al. *J Drugs Dermatol.* 2021;20(10):1076-1084.
2. Jublia® (efinaconazole topical solution, 10%). Full Prescribing Information. Bausch Health Companies, Inc; 2020.
3. Penlac® (ciclopirox topical solution, 8%). Full Prescribing Information. Sanofi-Aventis US, LLC; 2006.
4. Kerydin® (tavaborole topical solution, 5%). Full Prescribing Information. PharmaDerm; 2018.
5. Elabbasi A, et al. *Dermatol Ther (Heidelb).* 2024;14(9):2495-2507.
6. Vlahovic TC. *Clin Podiatr Med Surg.* 2016;33(3):305-318.
7. Gamal A, et al. *J Am Podiatr Med Assoc.* 2024;114(5):1-30.
8. Jo Siu WJ, et al. *Antimicrob Agents Chemother.* 2013;57(4):1610-1616.
9. Rezaei-Matehkolaei A, et al. *Antimicrob Agents Chemother.* 2018;62(5):e02423-17.
10. Tachibana H, et al. *J Fungi (Basel).* 2017;3(4):58.
11. Taghipour S, et al. *Infect Drug Resist.* 2020;13:845-850.
12. Elewski BE, et al. *J Am Acad Dermatol.* 2013;68(4):600-608.
13. Elewski BE, et al. *J Am Acad Dermatol.* 2015;73(1):62-69.
14. Matsuda Y, et al. *PLoS One.* 2016;11(7):e0159661.
15. Sugiura K, et al. *Antimicrob Agents Chemother.* 2014;58(7):3837-3842.
16. Vlahovic TC, Gupta AK. *Expert Rev Anti Infect Ther.* 2022;20(1):3-15.

AUTHOR DISCLOSURES

Ali Elabbasi and Ahmed Kadry have nothing to disclose. Warren Joseph has served as consultant and speaker for Ortho Dermatologics. Boni Elewski has provided clinical research support (research funding to University) for AbbVie, Anaptys-Bio, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Incyte, LEO Pharma, Lilly, Merck, Menlo, Novartis, Pfizer, Regeneron, Sun Pharma, Ortho Dermatologics, and Vanda and as consultant (received honoraria) from Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, LEO Pharma, Lilly, Menlo, Novartis, Pfizer, Sun Pharma, Ortho Dermatologics, and Verrica. Shari Lipner has served a consultant for Ortho Dermatologics, Eli Lilly, Moberg Pharmaceuticals and BelleTorus Corporation. Eric Guenin is an employee of Ortho Dermatologics and may hold stock and/or stock options in its parent company. Mahmoud Ghannoum has acted as a consultant or received contracts from Bausch & Lomb, Mycovia, Pfizer, and Scynexis, Inc.

ACKNOWLEDGEMENTS: Medical writing support was provided by Prescott Medical Communications Group, a Citrus Health Group, Inc., company (Chicago, Illinois), with financial support from Ortho Dermatologics; Ortho Dermatologics is a division of Bausch Health US, LLC • *Presented at Winter Clinical Dermatology Conference - Miami 2025 • January 17-20, 2025 • Miami Beach, FL*