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CLINICALLY SPEAKING

Total Dystrophic Onychomycosis Successfully Treated with Efinaconazole Topical Solution in Times of COVID: A Case Study

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Toenail onychomycosis is a common condition that is equally challenging for podiatrists and patients. This case study documents a 26-year-old woman with bilateral total dystrophic onychomycosis of at least 5 years' duration. She had previously failed to respond to treatment with ciclopirox nail lacquer 8% and despite hiding her condition with nail polish, was suffering from embarrassment, distress and low self-esteem. At initial consult, one hundred percent of both great toenails were affected. After discussion of all treatment options, the patient opted for topical efinaconazole 10% solution, once daily for 48 weeks. Significant improvement was noted at the first (4 week) assessment period. This improvement was maintained through each subsequent virtual consult and complete cure was seen at a 30-week follow-up visit. To the author's knowledge this is the first published report on the use of efinaconazole in total dystrophic onychomycosis. It suggests that the product may be effective in patients with even

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the most severe and treatment recalcitrant disease, who are unwilling or unable to tolerate systemic antifungal therapy.

Onychomycosis is a progressive fungal infection of the nail bed, matrix, or plate that may lead to destruction and deformity of the toenails or fingernails.^{1,2} It is caused by dermatophytes, yeasts or non-dermatophytic moulds.³ The dermatophytes *Trichophyton rubrum*, *Trichophyton mentagrophytes* and *Epidermophyton floccosum* are the main causative pathogens, responsible for approximately 90% of cases.³

Although not life-threatening, it may negatively affect a person's self-esteem and quality of life due to the reaction of others to their visible nail dystrophy or the perception that others find it to be unsightly or associated with poor personal hygiene.⁴⁻⁶

Toenail onychomycosis is particularly challenging to treat because of slow nail growth, and the physical properties of the nail unit that impede topical drug penetration.^{7,8} Both topical and oral agents are available for the treatment of fungal nail infection, but have relatively limited therapeutic success, particularly long-term. Historically, oral medications such as terbinafine and itraconazole have been recommended as first line therapy, especially in severe disease, but are associated with high recurrence rates and are not suitable for many patients due to drug interactions and systemic side effects, including headache, gastrointestinal disturbance and hepatotoxicity.^{9,10} Topical treatment may be preferable to patients as they reduce the likelihood of side-effects and/or the requirement for laboratory monitoring, but are

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typically only recommended for mild to moderate cases.^{11,12} However, the treatment paradigm is changing.¹³ Newer topical therapies have been shown by network meta-analysis to improve the odds ratio of mycological cure - defined as negative potassium hydroxide (KOH) test and negative culture.^{14,15} The efficacy of these new agents was also noted by a 2015 joint podiatric medicine-dermatology roundtable and previously reported in this journal.¹⁶ One of the newer antifungal options, efinaconazole topical solution 10% (Jublia, Ortho-Dermatologics; Bridgewater, New Jersey) is a topical imidazole active against both dermatophytes and yeasts. Its low affinity for keratin and low surface tension enables it to better penetrate the nail plate and selectively target pathogenic fungi.¹⁷ An in vitro study demonstrated that a single dose of efinaconazole 10% solution achieved a mycological eradication rate of 42.9%. This study also showed no difference in the concentrations seen in normal or affected nails or in the concentrations measured in the first and second toenails suggesting that transungual delivery and accumulation is not influenced by either presence of fungal disease or nail thickness.¹⁸ Studies have also shown that efinaconazole can penetrate the nail following the application of nail polish resulting in similar concentrations as those seen in control specimens free of polish.^{19,20}

The safety and efficacy of once daily use of efinaconazole for the treatment of toenail onychomycosis was evaluated in two prospective, multi-center, randomized, double-blind clinical trials in patients 18 years and older.²¹ Patients were treated with active agent or vehicle

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for 48 weeks. Complete cure, defined as 0% involvement of the target toenail, and mycological cure were assessed at Week 52.

In study 1, complete cure was achieved in 17.8% (117/656) of efinaconazole treated subjects versus 3.3% (7/214) with vehicle. Mycologic cure was achieved in 55.2% (362/656) of efinaconazole treated subjects versus 16.8% (36/214) with vehicle.

In study 2, complete cure was achieved in 15.2% (88/580) of efinaconazole treated subjects versus 5.5% (11/201) with vehicle. Mycologic cure was achieved in 53.4% (310/580) of efinaconazole treated subjects versus 16.9% (34/201) with vehicle.

It is worth noting that none of the subjects in these two studies had >50% involvement of the target toenail. Overall, 74.8% of subjects were graded as moderate severity at baseline and 25.8% had a severity rating of mild.

A 2019 study looked at long-term (72-week) treatment with efinaconazole. Of the 219 subjects 80 (36.5%) had >50% clinical involvement of the target nail. Complete cure rate at the final assessment in the patient population with clinical nail involvement of more than 50% was 38.8% versus 69.9% in patients with 20-50% involvement (n=139).²²

However, an extensive literature search failed to elicit any studies or even prior case reports on the use of efinaconazole in patients with total dystrophic onychomycosis.¹² This form of onychomycosis is a late stage of the chronic subungual dermatophyte infection that may take years to develop. It is not only the most difficult stage to clear but is also the type

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with the highest risk of associated subungual ulceration, secondary bacterial infection and possible gangrene.²³

With the arrival of COVID-19 and stay-at-home orders instituted across the country, many podiatrists, this author included, pivoted to telemedicine as a way to remain engaged with patients. Although telehealth and podiatry may not seem to go hand in hand, the reality is, they are perfectly matched. Through virtual and asynchronous consults with real-time, audio-video communication I was able to connect with both new and existing patients, some from geographically remote locations. And while the global COVID-19 pandemic caused some people to delay seeking non-COVID-related care,²⁴⁻²⁶ it afforded others, including the patient described in this report, the opportunity to seek care for chronic conditions that they had been hitherto ignoring.

Case Report

The patient is a healthy 26-year-old female, with no significant past medical history and currently on no medications. She presented for a virtual telemedicine consult in May 2020, during the COVID-19 pandemic, with bilateral 100% totally opaque great toenails. She had been diagnosed with onychomycosis five years earlier by a podiatrist in New York City, based on an in-office periodic acid Schiff (PAS) stain that revealed the dermatophytic fungus *Trichophyton rubrum*. At that time, she was treated with topical ciclopirox nail laquer 8% but became non-compliant after she failed to elicit any response over a period of five months.

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Virtual visual examination revealed thickened, crumbling, opaque nails on her great toes, with no involvement of other toenails or tinea pedis (Figure 1). There was no evidence of subungual hyperkeratosis or detachment of the nail from the nail bed (onycholysis). However, the involvement of the entire nail apparatus, the diffuse thickening and the friability of her nails was suggestive of the most severe clinical subtype - total dystrophic onychomycosis.²⁷ Additionally, erythema of the surrounding skin suggested development of a secondary bacterial infection.

Differential diagnoses, including nail psoriasis, lichen planus, pachyonychia congenital and the “disappearing nail bed” - onycholysis secondary to onychomycosis in which the nail bed appears to shrink, become keratinized and produce dermatoglyphics²⁸ were considered, but the totality of the patient’s history and the exam findings supported the presumptive diagnosis. Overall the nails appeared well maintained by the patient. A focused history revealed that she typically covered them with toenail polish so as to hide her embarrassment about the disease process. She denied pain or paresthesia, but admitted to some discomfort when wearing dress shoes.

A discussion ensued that covered all aspects of the treatment choices available to the patient. This included surgical, oral, and topical treatment plans. Because of her previous non-compliance, adherence to any of these treatment plans was an issue that was discussed at length.

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As she was concerned about the potential for side effects of systemic treatment, it was determined that efinaconazole would be in the patient's best interests at this time. The decision was made with the patient fully aware of the scientific data and that the severity of her condition fell outside of the previously studied treatment parameters for this product.

She was instructed to apply efinaconazole to the affected toenails once a day for 48 weeks, at least 10 minutes after showering, bathing, or washing, in accordance with the manufacturers package instructions. To prevent recurrence, she was advised to trim her great nails as they grew out, dry her feet completely after showering and swimming, and to wear shoes in public areas. Additionally, she was taught how to tape her affected toes, starting at the point where the nail meets the skin distally, down and around the plantar pulp of the toe, to encourage the skin to flatten and allow the nail to grow over the skin as recommended by Vlahovic et al.²⁸

At a virtual follow-up consult thirty days after starting efinaconazole there was significant improvement in the appearance of her toenails and the surrounding skin (Figure 2). The change in clinical involvement can be calculated using the following formula: Changes in clinical involvement = clinical involvement at baseline – clinical involvement after application of efinaconazole.

At 30 days the change in clinical involvement was calculated to be 30%, at 60 days (8.5 weeks) 55% (Figure 3), at Day 120 (17 weeks) 80% [Figure 4]; at Day 150 (21.4 weeks) 90% [Figure 5] and at Day 210 (30 weeks) 100%, which represents complete clinical cure. [Figure 6].

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No adverse drug reactions have been reported during treatment. The patient rated treatment satisfaction as 100% and noted dramatic improvement in confidence and social interactions. She will continue to treat to 48 weeks.

Discussion

Onychomycosis is one of the conditions most frequently encountered by podiatrists. Although this patient and many others seek onychomycosis treatment primarily for cosmetic purposes, it is critical that it is successfully treated to prevent cross-contamination to close personal contacts, secondary complications such as tinea pedis and decreased quality of life due to embarrassment about the aesthetic appearance of their nails.

Prior to the COVID-19 pandemic, clinical examination, dermoscopy and mycological examination were considered standard of care for all patients with suspected onychomycosis, followed by a discussion of appropriate treatment options. However, since the emergence of COVID-19, pre-pandemic guidelines are no longer applicable. Many patients had to deal with lock downs, stay-at-home orders, quarantine or isolation. Some podiatrist offices closed while for others, non-urgent in-person visits were replaced by telemedicine. The latter solution proved ideal for this tech-savvy, young patient who had prior mycological confirmation of her condition. It allowed for accessible and quality care, an initial consult devoid of the usual embarrassment associated with onychomycosis and more frequent follow-up video visits, all while limiting the risk for COVID-19 transmission. As toenails grow approximately 1 mm/month,

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I normally perform follow-up on patients being treated with topicals every 3-months which allows the degree of proximal clear nail to be measured. However, given the convenience of telemedicine and the patient's history of treatment non-adherence, following her every thirty days contributed, at least partially, I suspect, to the successful outcome.

The efficacy can more directly be attributed to the fact that efinaconazole both inhibits the fungal cytochrome P450 enzyme and blocks fungal membrane ergosterol biosynthesis, thereby disrupting the membrane integrity and growth of fungi²⁹ and has relatively low binding to keratin which enables nail penetration.^{17,18,30}

The rapid and sustained improvement experienced by this patient treated with the triazole antifungal efinaconazole is consistent with that seen in previous controlled clinical studies of mild and moderate toenail onychomycosis.^{17,21,22} The absence of systemic or local side-effects in this patient is also consistent with the findings from a pooled analysis of Phase III clinical trial participants which revealed that treated-related side effects were similar to vehicle and limited to local site reactions (2%).³¹ However there appear to be no studies or other publications of efinaconazole in patients with total dystrophic onychomycosis.

Conclusions

While systemic therapy is generally considered the gold standard in severe fungal toenail disease, this case, treated by telemedicine, during the COVID-19 pandemic, suggests that there

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may be a role for efinaconazole in total dystrophic onychomycosis. Further studies would be needed to confirm this.

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References

1. Scher RK, Coppa LM. Advances in the diagnosis and treatment of onychomycosis. *Hosp Med*. 1998;34:11–20.
2. Crissey JT. Common dermatophyte infections. A simple diagnostic test and current management. *Postgrad Med*. 1998;103(2) 191-1,197-200,205.
3. Welsh O, Vera-Cabrera L, Welsh E. Onychomycosis. *Clin Dermatol*. 2010 Mar 4;28(2):151-9.
4. Drake LA, Patrick DL, Fleckman P, et al. The impact of onychomycosis on quality of life: development of an international onychomycosis questionnaire to measure patient quality of life. *J Am Acad Dermatol*. 1999;41:189–196.
5. Scher RK. Onychomycosis: a significant medical disorder. *J Am Acad Dermatol*. 1996;35(3 Pt 2):S2–S5.
6. Lubeck DP, Patrick DL, McNulty P, et al. Quality of life of persons with onychomycosis. *Qual Life Res*. 1993;2:341–348.

This Clinically Speaking has been reviewed, accepted for publication, and approved by the author. It has not been copyedited, proofread, or typeset and is not a final version.

7. Finch JJ, Warshaw EM. Toenail onychomycosis: current and future treatment options.

Dermatol Ther. 2007 Jan-Feb;20(1):31-46.

8. Del Rosso JQ. Onychomycosis of Toenails and Post-hoc Analyses with Efinaconazole 10%

Solution Once-daily Treatment: Impact of Disease Severity and Other Concomitant Associated

Factors on Selection of Therapy and Therapeutic Outcomes. *J Clin Aesthet Dermatol.*

2016;9(2):42-47.

9. Shirwaikar AA, Thomas T, Shirwaikar A, Lobo R, Prabhu KS. Treatment of onychomycosis: an

update. *Indian J Pharm Sci.* 2008;70(6):710-714.

10. 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.

11. Kawa N, Lee KC, Anderson RR, Garibyan L. Onychomycosis: A Review of New and Emerging

Topical and Device-based Treatments. *J Clin Aesthet Dermatol.* 2019;12(10):29-34.

12. Foley K, Gupta AK, Versteeg S, Mays R, Villanueva E, John D. Topical and device-based

treatments for fungal infections of the toenails. *Cochrane Database Syst Rev.*

2020;1(1):CD012093. Published 2020 Jan 16. doi:10.1002/14651858.CD012093.pub2

13. Aggarwal R, Targhotra M, Kumar B, Sahoo PK, Chauhan MK. Treatment and management

strategies of onychomycosis. *J Mycol Med.* 2020 Jun;30(2):100949.

14. Gupta AK, Daigle D, Foley KA. Network Meta-Analysis of Onychomycosis Treatments. *Skin*

Appendage Disord. 2015 Sep;1(2):74-81.

This Clinically Speaking has been reviewed, accepted for publication, and approved by the author. It has not been copyedited, proofread, or typeset and is not a final version.

15. Gupta AK, Daigle D, Paquet M. Therapies for onychomycosis a systematic review and network meta-analysis of mycological cure. *J Am Podiatr Med Assoc.* 2015 Jul;105(4):357-66.
16. Markinson BC, Vlahovic TC, Joseph WS, Scher RK, Tosti A, Plasencia J, Pariser DM. Diagnosis and Management of Onychomycosis: Perspectives from a Joint Podiatry-Dermatology Roundtable. *J Am Podiatr Med Assoc.* 2015 Sep 25.
17. Lipner SR, Scher RK. Efinaconazole 10% topical solution for the topical treatment of onychomycosis of the toenail. *Expert Rev Clin Pharmacol.* 2015;8(6):719-31.
18. Sakamoto M, Sugimoto N, Kawabata H, Yamakawa E, Koder N, Pillai R, Tatsumi Y. Transungual delivery of efinaconazole: its deposition in the nail of onychomycosis patients and in vitro fungicidal activity in human nails. *J Drugs Dermatol.* 2014 Nov;13(11):1388-92. PMID: 25607707.
19. Zeichner JA, Stein-Gold L, Korotzer A. Penetration of (14C)-efinaconazole topical solution, 10%, does not appear to be influenced by nail polish. *J Clin Aesthet Dermatol.* 2014;7(9):34–36.
20. Del Rosso JQ. Application of nail polish during topical management of onychomycosis: are data available to guide the clinician about what to tell their patients? *J Clin Aesthet Dermatol.* 2016;9(8):29–36.
21. 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):600-608.

This Clinically Speaking has been reviewed, accepted for publication, and approved by the author. It has not been copyedited, proofread, or typeset and is not a final version.

22. Iozumi K, Abe M, Ito Y, et al. Efficacy of long-term treatment with efinaconazole 10% solution in patients with onychomycosis, including severe cases: A multicenter, single-arm study. *J Dermatol*. 2019;46(8):641-651. doi:10.1111/1346-8138.14935
23. Bodman M. Keys to Managing Severe Onychomycosis. *Podiatry Today* 2013;26(5):46-57
24. Sud A, Jones ME, Broggio J, et al. Collateral damage: the impact on outcomes from cancer surgery of the COVID-19 pandemic. *Ann Oncol* 2020;31:1065-74.
25. Mihaljevic T, Farrugia G. How many more will die from fear of the coronavirus? *New York Times* 2020 Jun 9. <https://www.nytimes.com/2020/06/09/opinion/coronavirus-hospitals-deaths.html>. Accessed February 19, 2021.
26. Solomon MD, McNulty EJ, Rana JS, et al. The covid-19 pandemic and the incidence of acute myocardial infarction. *N Engl J Med* 2020;383:691-3.
27. Hay RJ, Baran R. Onychomycosis: a proposed revision of the clinical classification. *J Am Acad Dermatol*. 2011 Dec;65(6):1219-27. doi: 10.1016/j.jaad.2010.09.730. Epub 2011 Apr 17. PMID: 21501889.
28. Vlahovic T, Borrelli A, Bruno J. How to Address The Disappearing Nail Bed. *Podiatry Today* 2021;34,2:26-29
29. 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*.

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2013 Apr;57(4):1610-6. doi: 10.1128/AAC.02056-12. Epub 2013 Jan 14. PMID: 23318803;
PMCID: PMC3623347.

30. Lee BC, Pangeni R, Na J, Koo KT, Park JW. Preparation and *in vivo* evaluation of a highly skin- and nail-permeable efinaconazole topical formulation for enhanced treatment of onychomycosis. *Drug Deliv*. 2019;26(1):1167-1177. doi:10.1080/10717544.2019.1687612

31. Gupta AK, Elewski BE, Sugarman JL, Ieda C, Kawabata H, Kang R, Pillai R, Olin JT, Watanabe S. The efficacy and safety of efinaconazole 10% solution for treatment of mild to moderate onychomycosis: a pooled analysis of two phase 3 randomized trials. *J Drugs Dermatol* 13: 815, 2014.

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Figure 1. Baseline - Day 1

Figure 2. Day 30

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Figure 3. Day 60

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Figure 4. Day 120

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Figure 5. Day 150

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Figure 6. Day 210