DISCLAIMER: Dieter J. Fellner is an independent contractor in private practice in NYC. A Clearanail unit was purchased with private funds to evaluate the technology. Dr. Fellner has no vested financial interests in Clearanail or Ex-It Medical Industries.

Background

Onychomycosis is a significant concern in the podiatry clinic. Prevalence of fungal nails in the population is estimated to be 2-8% in the western world. Authors suggest this number may be as high as 14% of adults in North America affecting 35 million Americans leading to 11.2 million office visits each year. Onychomycosis accounts for about 50% of all nail disease. With many more cases unreported, the true prevalence is thought to be much higher. Common treatment options include debridement, surgical removal, and pharmacological agents (topical, systemic). In addition, there are newer treatments such as micro-drilling, a unique way to deliver topical drugs through the nail plate into the nailbed.

Sometimes marginalized as merely a cosmetic concern, the effect of onychomycosis on quality of life (QoL) is well documented. The fungal nail infection is a chronic disease and can have a psychological impact, contribute to pain and affect ambulation. When there is co-morbidity, e.g., diabetes mellitus, PVD, the immunocompromised, there is an even greater urgency to treat. In a patient with diabetes mellitus the prevalence of onychomycosis is 2.8 times greater and can contribute to serious bacterial infection and foot ulceration.

Onychomycosis: Treatment

80% of podiatrists perceive that an oral anti-fungal is the most effective treatment but recommend them in only 30% of cases. A topical anti-fungal is perceived as effective by 7% of podiatrists but used in 48% of cases. Based on an FDA trial, the cure and success rates using ciclopirox, one such popular topical anti-fungal, were 8.5% and 12% respectively. Surgical removal of the nail, with excision of the nail matrix, can provide a permanent solution but may be an unacceptable option for a patient seeking a cosmetically acceptable outcome. Simple avulsion, without matrixectomy, poses a risk of reinfection and a re-growth consisting of an iatrogenic dystrophic nail.

Is Testing Still Required Before Prescribing for Oral Terbinafine?

Terbinafine is perhaps the most widely-prescribed oral anti-fungal drug. The absolute requirement for blood tests and fungal culture was recently challenged in a Harvard study, suggesting empirical terbinafine should be prescribed routinely without benefit of culture. Liver toxicity

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induced by oral terbinafine has likely been over-reported and occurs in as few as 1:50,000—1:100,000 treatments, with even rarer instances of durable clinical sequela. Most strikingly, the analysis reveals, it would take up to $90.2 million of PAS testing to prevent a single case of clinically relevant hepatotoxicity from oral terbinafine.\textsuperscript{11}

The use of a hand-held dermatoscope can, in addition, significantly improve clinical diagnosis. The so-called aurora borealis pattern of linear longitudinal dermatophytic spikes found with the dermatoscope correlates highly with mycological testing.\textsuperscript{12}

Pretreatment confirmation of onychomycosis before prescribing terbinafine may no longer be necessary. Important caveats, to this conclusion, include fungal species identification using PCR (e.g., yeast and saprophytes respond better to fluconazole, itraconazole). Ultimately, each practitioner must decide his or her comfort zone with systemic vs. topical approaches to patient care.

**Topical Agents**

For newer technologies, activity has focused primarily on topical agents, hydrophilic and low in molecular weight to improve transport technology and better penetrate the nail. The pharmacology industry undoubtedly has made a substantial effort to deliver ever more efficacious agents. Yet the in-vitro efficacy of the anti-fungal agent has yet to be matched with comparable in-vivo outcomes. The daily application of topical medication continues to require patient compliance for the course of one year or more.

**The Role of Nail Trephination in Drug Delivery**

For the last few years there have been few significant advances in the ongoing struggle to treat onychomycosis more quickly and effectively.

As reported by Podiatry Today in November of 2007, the novel idea of drug delivery to the nail using trephination or “mesoscissioning” was first introduced using Pathformer (Path Scientific, USA), a handheld device, that uses a microscopic cutter to penetrate the nail plate but not the nail bed. The principal of this device is based on electrical impedance, effectively decreasing the inherent electrical potential of the epidermis, a known insulator. This idea allows drugs to enter the “stratum corneum-free” nailbed painlessly. A Phase 1 study conducted at Bringham and Women’s Hosp-
tal found the procedure to be painless, offering both depth control and a mycological cure in a diverse patient population. Of interest, a terbinafine 1% cream was applied to the nails, in direct contrast to today’s standard of care with low molecular weight, hydrophilic solutions widely preferred.13

A recent study from Shemer and Gupta AK, in Israel presents a noteworthy exception. The work reveals an open comparative study of nail drilling by trephine, as an adjunctive treatment for toenail onychomycosis.14

Presented as a parallel three-arm trial the study investigates the effects, outcome and safety of treatment using trephine technology. A total of 106 nails (98 patients) are evaluated comprising of three treatment groups.

**Group 1:** was provided trephined holes plus topical and oral terbinafine. **Group 2:** consisted of trephination plus topical terbinafine. **Group 3:** was treated with topical terbinafine only. Outcome measures include clinical and mycological cure rates, evaluated at 4, 10, 16, 22 and 28 weeks.

The study concludes that both groups managed concurrently with trephined holes in the nails had a significantly higher percentage of clear nail compared with topical terbinafine alone. Interestingly, the addition of oral terbinafine provided no significant advantage with comparable out-

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**Figure 4:** Comparison of Clearanail 0.4mm and a 1.8mm drill (image courtesy of Dr. R. Thomas)

**Figure 5:** Clearanail micropore trephination (image courtesy of Dr. I. Bristow)

**Figure 6:** Clearanail micropore trephination (image courtesy of Dr. I. Bristow)

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comes between Group 1 and Group 2. Treatment of fungal nails with holes plus topical terbinafine produces greater improvement in the appearance of the toenail and a higher, and significantly earlier, mycological cure rate.

For nail trephination, the Israeli study used an ingenious apparatus, an automatic device manufactured by Ex-It Medical Devices Ltd. This is used to drill two horizontal lines of holes just proximal to the border between the diseased and healthy segment of the nail. Holes are of a 1.8mm diameter, spaced 2mm apart. Grossly, the nail plate consists of a superficially dry compartment and a deeper humid department. This trephine technology is designed to detect when the drill has reached the more humid department. When a pre-defined humid level is reached the drill aborts, to protect against pain and nail bed injury. Nail trephination is required one time only. After this work, data analysis confirms that no case of bleeding or pain was reported.

In the August 2016 issue of Journal of Drugs and Dermatology, Ivan Bristow, PhD and Robert Baran, MD, reported further treatment success in 3 case studies of onychomycosis, using controlled micro-nail penetration delivered by a U.K. device known as Clearanail. The authors further hypothesize that a “subungual mass of dermatophyte hyphae which are not attached to the nail bed or nail plate remain shielded by the overlying nail plate.” This presence of a dermatophytoma slows the passage of low-tension anti-fungal solution without the adjunct of micro-drilling. Terbinafine 1% spray is readily available in worldwide retail settings at a very low cost.15

**Trephination Technology & The United Kingdom Initiative**

In 2016, the Clearanail device, invented and patented in the UK, was introduced to the North American Market. Clearanail® (Medical Device Treatment Ltd., Brighton, UK) is based on a simple but “intelligent” nail drill design. This consists of a unit and handpiece and is fitted with a single-use 0.4mm carbide micro-cutter to provide for controlled nail micro-penetration to bore many holes directly into the nail plate. The drill safely stops once it is through the nail plate and before damaging the underlying soft tissue of the nail bed. Sterile Single Use Micro-cutters (SUMS), roughly the size of a 27 Gauge needle, must be bought and used individually. The nail is rendered permeable, providing channels for rapid delivery of drugs to the nail plate and nail bed to target the antifungal effect at the source of the

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dermatophyte infection. It is hypothesized the presence of the air gap facilitates the passage of low-tension anti-fungal solutions such as terbinafine 1% solution. Weight-bearing provides for lateral spread of the anti-fungal medication aided by downward counter-pressure from the nail plate.16

Can “Micro-drilling” Live Up To Patient Expectations?

Early adopters of micro-drilling report encouraging results. Although there is no reason to suspect a problem, it is unclear yet if the treatment can be effective for all types & grades of mycotic infection. Anecdotal and case reports26 are encouraging but there are no published randomized, prospective trials to further evaluate Clearanail”.17

Clearanail” is a technologically enhanced and better-tolerated trephine technique. It is a safe and painless, turbo-charged drug-delivery system to the affected nail and nail bed, via ‘micro-pores’. The delivery of up to twenty 0.4mm micro-pores is permanent until the nail grows out and somewhat visible, but not a cosmetic disaster, until the nail re-grows.

Onychomycosis is a chronic disease. Effectiveness of the treatment will, ultimately, also require good patient compliance with regular and persistent application of anti-fungal medication. Re-infection is a constant risk, and diligent, regular anti-fungal management of skin, footwear and hosiery must be observed.

A “silver-bullet” promise will inspire, in a patient, high expectations: “a one-off, immediately effective and permanent cure of the infection with restoration of a normal healthy, cosmetically appealing nail plate.” A patient’s expectations, as is often the case, will need to be tempered and rendered realistic. 50% of nail disease is onychomycosis. Can micro-drilling be further studied in other drug delivery models to perhaps improve psoriasis or nail barrier dysfunction?14 The severely dystrophic nail may still require, from a patient standpoint, weeks of ongoing topical treatment. The outcome may be rendered suboptimal when it is dependent on daily patient-administered treatments.

The combined scientific and anecdotal evidence to date for treatment, augmented with nail trephination, is promising. The Israeli study firmly points to the fact that nail trephination is a valuable adjunctive measure. As yet there are no similar prospective, randomized, comparative trials for Clearanail”. Further research can provide information, to know also if variation in drill size and depth can provide an additional treatment advantage. Trephination as a concept, it seems, would certainly provide a podiatrist with a very useful and welcome addition to the tool-box. PM

References