

# Patient considerations in the management of toe onychomycosis – role of efinaconazole

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**Abstract:** Onychomycosis is a difficult diagnosis to manage and treatment is sometimes avoided, as this diagnosis is often wrongly perceived as a cosmetic problem. However, onychomycosis has a negative impact on patients' quality of life, affecting social interaction, psychological well-being, and physical activities. Onychomycosis is also a risk factor for patients with diabetes, with proven increased rates of cellulitis, gangrene, and foot ulcers. Treatments are only mild to moderately effective, and rates of relapse and reinfection are high. Oral treatments require laboratory monitoring due to risk of hepatotoxicity and may be contraindicated in some patients due to risk of drug–drug interactions. Topical treatments require prolonged application and are not very effective. Efinaconazole 10% solution is a new topical triazole treatment for mild to moderate distal subungual onychomycosis, with good efficacy and without the need for debridement of nails. In onychomycosis of the toenails, efinaconazole 10% solution is documented to have a statistically significant, positive impact on patient satisfaction and quality of life.

**Keywords:** nail, fungus, quality of life, treatment, antifungal, dermatophyte

## Introduction

Onychomycosis describes a common infection of the nail unit by dermatophytes, yeasts, or nondermatophytic molds that affects the toenails more frequently than fingernails.<sup>1</sup> The negative impact on patients is more than cosmetic. Although this is often wrongly perceived as a superficial problem, there can be a significant impact on quality of life (QOL).<sup>2,3</sup> When compared to healthy individuals, persons with onychomycosis had significantly lower ratings on assessment of self-perception of general health, bodily pain, mental health, social functioning, health concern, physical appearance, and functional limitations in activities on foot.<sup>3</sup> Sequela of the disease include pain and discomfort,<sup>4</sup> spread to other nails in the same patient or to the skin and nails of other family members,<sup>4–6</sup> and increased risk of bacterial infections, such as cellulitis, particularly in patients with diabetes.<sup>7,8</sup> Patients with diabetes and onychomycosis are at a three-fold higher risk of developing complications such as foot ulcer and gangrene compared to diabetic patients without onychomycosis.<sup>9</sup> Nearly 90% of patients desire treatment, and 41% are even willing to accept treatment-associated side effects in order to be treated.<sup>3</sup>

Many nail dystrophies may mimic onychomycosis clinically, so it is important that a definitive diagnosis be established to avoid unnecessary costs or complications of treatment.<sup>10</sup> Treatment of onychomycosis should only be performed after clinical assessment and microbiologic confirmation of the presence of hyphae or spores via KOH examination of scrapings of the nail bed, fungal culture, polymerase chain reaction, and/or microscopic examination, which may include periodic acid–Schiff stain of a nail clipping.<sup>11,12</sup>

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Onychomycosis of the toenails is difficult to treat, and recurrence rate after cure is high.<sup>13</sup> Systemic therapies are more effective than topical therapies, but their use can be limited by risk of drug interactions and systemic side effects. Patients often prefer and request topical treatments; however, penetration of the nail plate is difficult and the overall efficacy is lower than with systemic therapy.

The US Food and Drug Administration (FDA) recently approved efinaconazole, a topical antifungal, for the treatment of mild to moderate distal subungual onychomycosis (DLSO) of the toenails, defined as 20%–50% involvement of the target toenail.<sup>14</sup> The objective of this article is to review onychomycosis from a patient-focused viewpoint and to discuss the efficacy and safety of efinaconazole.

## Onychomycosis basics

Dermatophyte fungi are the most common culprits in onychomycosis, with *Trichophyton rubrum* and *Trichophyton mentagrophytes* species isolated in 80%–90% of cases.<sup>15,16</sup> However, nondermatophyte fungi such as *Scopulariopsis brevicaulis*, *Fusarium* spp., and *Aspergillus* spp. can also contribute, especially in Europe and South America.<sup>17</sup> Tinea pedis is a common dermatophyte infection of the foot that is often associated with onychomycosis,<sup>18</sup> where the dermatophyte causing tinea pedis is thought to spread from the sole to the nails.<sup>19</sup>

There are several subtypes of onychomycosis.<sup>20–22</sup> DLSO is the most common type, usually due to *T. rubrum*, and most commonly involves the first toe. Fungi reach the nail bed through the hyponychium causing subungual hyperkeratosis and onycholysis; proximal spreading often occurs with yellow-white streaks. The nail plate shows yellow-white discoloration. Proximal subungual onychomycosis (PSO) is much less common and starts proximally at the cuticle and moves distally. PSO due to *T. rubrum* may be a marker of severe immune suppression, such as AIDS.<sup>23,24</sup> White superficial onychomycosis is most commonly due to *T. mentagrophytes* and is an infection of the superficial nail plate. It appears as dull white spots on the nail plate surface that spread centrifugally and may involve one or several nails. The white areas easily scrape off with light curettage.

## Limitations of therapy

Treatment options for onychomycosis are limited in number and efficacy. Relapse due to incomplete treatment and reinfection can occur in up to 25% of patients,<sup>13</sup> with many suffering a long history of disease recurrence.<sup>25</sup> In the United States, the only approved treatments for onychomycosis include topical ciclopirox, and systemic terbinafine and

itraconazole. Topical amorolfine is available in Europe and South America but not in the United States. Systemic antifungals are more effective than topical antifungals, but their use can be limited by possible drug–drug interactions (DDIs) and side effects.<sup>26</sup> Topical ciclopirox has limited efficacy and requires a long treatment period of up to 48 weeks of daily application and debridement. Some authors suggest to combine oral antifungals with topical treatment and nail debridement<sup>27</sup> or avulsion<sup>28</sup> to decrease duration of therapy and likelihood of adverse effects. Sometimes, physicians discourage patients from undergoing treatment, despite patient desire, as they are concerned of possible side effects, limited efficacy, and frequent relapse.<sup>3</sup>

Choice of treatment regimen should be based on patient health, associated disease, and severity of onychomycosis. Topical therapy is appropriate for mild to moderate DLSO and as initial treatment of classic white superficial onychomycosis. Some doctors also prescribe topical therapy to patients who have already reached clearance with oral therapy in order to prevent reinfection.<sup>29</sup> It may also be combined with systemic treatment in order to increase success rate.

## Barriers to the use of systemic therapies

Approved systemic therapies include oral terbinafine and oral itraconazole. Oral fluconazole, although effective, is not approved for this indication in the United States.<sup>30–33</sup> Most dermatologists consider terbinafine 250 mg daily for 3 months the “gold standard” treatment for onychomycosis.<sup>34</sup> Terbinafine is a safe medication, and side effects are uncommon, but cases of severe liver toxicity have been reported. Itraconazole is less frequently utilized as it is less effective than terbinafine<sup>35</sup> and has more drug interactions.<sup>15</sup> The approved dose for toenail onychomycosis is 200 mg daily for 3 months, but several studies show that an intermittent regimen of 400 mg daily for 1 week a month is also effective.<sup>35,36</sup> Fluconazole is utilized off-label as pulse therapy at a dosage of 150 or 300 mg once a week for several months (until cure).<sup>37</sup> This pulse regimen makes drug interactions and hepatotoxicity less common.

Terbinafine and itraconazole are not recommended for patients with active or chronic liver disease.<sup>15</sup> Monitoring of hepatic function is recommended prior to and during treatment for all patients, but especially in patients with underlying liver disease.<sup>15,34</sup> Thus, systemic therapies are not a good option for patients who are unwilling or unable to have routine follow-up.

Additionally, DDIs may occur with systemic therapies because itraconazole and fluconazole inhibit CYP3A4 and

terbinafine is an inhibitor of CYP2D6.<sup>15</sup> Therefore they may cause alterations in metabolism of other drugs. Upon review of the patient's medication list, the physician may not be able to prescribe a systemic therapy due to known DDIs.

Cost of therapy with oral antifungals has considerably decreased after patent expiration. The last cost analysis of onychomycosis (including cost of medication, medical management, and management of adverse reactions) was performed in 1999, and a summary of the values to achieve mycologic cure in each patient is summarized as follows: griseofulvin US\$4,917, itraconazole (continuous therapy) US\$2,072, itraconazole (pulse therapy) US\$1,072, terbinafine US\$1,042, and fluconazole US\$1,449.<sup>38</sup> The estimated medication cost for complete cure using ciclopirox lacquer is between US\$1,381 and US\$2,135;<sup>39</sup> however, with other medical and management costs, the estimated cost of complete cure increased to US\$17,029–US\$26,317.<sup>40</sup> The cost for complete cure using efinaconazole has not yet been estimated. However, it should be kept in mind that topical therapies for onychomycosis are often not covered by medical insurance. On a larger scale, approximately US\$43 million (1997 values) is spent per year on the management of onychomycosis to cover 13 million visits by 662,000 patients over the age of 65.<sup>41</sup>

Patient compliance is a barrier to treatment of onychomycosis because prolonged treatment is necessary as nail growth is a slow process. Problems are more common in children, the elderly, and immunocompromised patients.<sup>42,43</sup> Important determinants of compliance with oral antifungal medications include: duration of therapy, ease of swallowing, frequency of dosage, and number of pills per intake.<sup>44</sup> Overall compliance with oral medications (intermittent pulse itraconazole, intermittent terbinafine, continuous terbinafine) for the treatment of onychomycosis was found to be 45% due to adverse effects (30%), discontinuation after perceived progress (22%), and financial barriers (16%).<sup>45</sup> Another systematic review and meta-analysis found that 19% of patients discontinued oral itraconazole due to an adverse reaction and 1.5% discontinued due to hepatotoxicity.<sup>46</sup>

## Efficacy comparison

Phase III studies reported complete cure rates of 14% with itraconazole and 38% with terbinafine and mycologic cure rates of 54% and 70%, respectively (Sporanox package insert; Janssen Pharmaceuticals, Inc., NJ, USA; Lamisil package insert; Novartis, Basel, Switzerland). Subsequently, mycological cure rates were studied in a meta-analysis and are as follows: terbinafine 76%±3%, itraconazole pulse therapy 63%±7%, griseofulvin 60%±6%, itraconazole continuous therapy

59%±5%, and fluconazole 48%±5%.<sup>47</sup> Reported clinical cure rates are similar to mean mycological cure rates but are harder to assess across trials as they often have varying definitions of cure and different follow-up periods.<sup>47</sup> Randomized clinical trials for ciclopirox lacquer have shown a complete cure rate of 5.5%–8.5% and a mycologic cure rate of 34%.<sup>48</sup>

Efinaconazole 10% solution, a topical triazole antifungal solution, is a new option for topical treatment of mild to moderate DLSO.<sup>14,49</sup> The vehicle of the solution contains alcohol, lipophilic esters, and cyclomethicone. Pooled data from two, multicenter, randomized, parallel-group, double blind, vehicle-controlled clinical trials<sup>50</sup> following 48 weeks of treatment showed complete cure (defined as 0% clinical involvement and mycologic cure with negative KOH examination and negative fungal culture) at week 52 in 18.5% of patients on efinaconazole versus 4.7% on inactive vehicle. Secondary end points were defined as mycologic cure, complete/almost complete cure (≤5% clinical involvement and mycologic cure), and treatment success (<10% clinical involvement of the target toenail), and unaffected new toenail growth. Mycologic cure was achieved in 56.3% on efinaconazole versus 16.6% with inactive vehicle. Complete or almost complete cure was obtained in 27.7% compared to 7.9% with inactive vehicle. Treatment success was seen in 47.2% compared to 18.2%. Mean unaffected new nail growth was higher with efinaconazole at 5.0 mm in study 1 and 3.8 mm in study 2 compared to 1.6 mm and 0.9 mm with inactive vehicle. Thus, efinaconazole 10% solution was significantly more effective for treating DLSO than inactive vehicle alone, and efficacy rates were two to three times greater than topical ciclopirox.

## Comparison of safety and time requirements

Efinaconazole has a broad spectrum of *in vitro* activity against dermatophytes, nondermatophytes, and yeasts. Efinaconazole 10% solution differs from topical antifungal lacquers because it is proven to penetrate well through the nail plate into the deeper nail layers and the nail bed due to a low keratin affinity.<sup>51</sup> Additionally, it is well tolerated with no systemic adverse effects reported in open-label studies, in both healthy volunteers and severe onychomycosis patients.<sup>52</sup> Reported side effects include application-site dermatitis and vesicles that have been attributed to the vehicle rather than the active ingredient.<sup>14</sup> Efinaconazole 10% solution has minimal systemic absorption. When applied to all ten toenails in severe DLSO patients and healthy volunteers, the maximum detected plasma concentration of efinaconazole and its H3 metabolite were negligible at 1.47 and 7.45 ng/mL, respectively.<sup>52</sup>

Topical treatments like efinaconazole need to be applied daily for several months. Thus, patient compliance is essential to achieve good results. Efinaconazole 10% solution needs to be brushed on the nail plate once daily for 48 weeks. In contrast to the systemic antifungals, efficacy and low toxicity come at the expense of long treatment duration and more daily time requirement. However, use of efinaconazole 10% solution is less time consuming than ciclopirox lacquer, which requires daily nail debridement and residual lacquer removal in addition to application time.

A recent study showed that use of nail polish does not reduce penetration of efinaconazole 10% solution, which is very important for female patients who do not want to show their affected nail when wearing sandals or going to the beach.<sup>53</sup>

## Comparison of patient satisfaction and quality of life after efinaconazole treatment

Efinaconazole 10% solution is documented to positively impact patient satisfaction and QOL in patients with onychomycosis of the toenails.<sup>54</sup> All aspects of QOL scores significantly improved as compared to vehicle. Additionally, improvement in QOL scores was greatest in patients who were considered clinically improved ( $\leq 10\%$  nail involvement at week 52) and correlated inversely with percent affected nail. Therefore, any positive change in nail health may positively impact patient-perceived QOL.<sup>54</sup>

## Conclusion

Though often regarded as a cosmetic problem, onychomycosis has a chronic, progressive course, with a significant burden of disease and negative impact on patient QOL. Treatments are historically limited in number and efficacy, with a high rate of relapse and recurrence. Oral antifungals are contraindicated in some cases as they carry risk of hepatotoxicity and DDIs. Disease prevalence is highest in the elderly, who are more likely to be on many medications and are at greatest risk for DDIs.

Efinaconazole 10% solution, a new triazole antifungal, was recently approved for treatment of mild to moderate DLSO of the toenails. The properties of low surface tension of the solution and low keratin affinity of the drug allow it to permeate the nail more readily and contribute to its efficacy. The mycologic and complete cure rates with efinaconazole are two- to three-fold greater than those of ciclopirox lacquer.

In addition to efficacy, efinaconazole 10% solution is safe, with little systemic absorption and remote potential for DDIs. Efinaconazole is well tolerated by the patient, and local side effects are uncommon. From the patient perspective,

efinaconazole 10% solution is proven to positively impact satisfaction and QOL. Treatment of onychomycosis is important as any improvement in nail health can have a positive effect on disease burden and patient QOL.

## Disclosure

Dr Tosti received honorarium from Valeant as consultant in advisory meetings. The authors report no other conflicts of interest in this work.

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