[REVIEW]

Risk Factors and Comorbidities for Onychomycosis

Implications for Treatment with Topical Therapy

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ABSTRACT

A number of comorbidities and risk factors complicate the successful management of onychomycosis. Underlying conditions and patient characteristics, such as tinea pedis, age, and obesity, contribute to risk, whereas comorbidities, such as diabetes and psoriasis, can increase susceptibility to the disease. There are limited data on treatment effectiveness in these patients. Here, the authors review *post hoc* analyses of efinaconazole topical solution, 10%, in mild-to-moderate onychomycosis and present new data in terms of age and obesity. The only *post hoc* analysis to report significant differences so far is gender, where female patients do much better; however, the reasons are unclear. The authors report significant differences in terms of efficacy in obese patients who do not respond as well as those with normal body mass index (P=0.05) and in patients who have their co-existing tinea pedis treated compared to those in whom co-existing tinea pedis was not treated (P=0.025). Although there is a trend to reduced efficacy in older patients and those with co-existing diabetes, differences were not significant. More research is needed in onychomycosis patients with these important risk factors and comorbidities to fully evaluate the treatment challengse and possible solutions.
(*J Clin Aesthet Dermatol.* 2015;8(11):38–42.)

Onychomycosis is a common problem in dermatology practice that can result in significant morbidity.[1,2] Successful treatment has been difficult because of slow growth of the nail; patient comorbidities, such as diabetes, peripheral vascular disease, and psoriasis; and reluctance of prescribers and patients to prescribe or take oral medications because of "perceived" toxicity issues.

The disease can have a major impact on the individual and other family members.[3–5] Dystrophic nails can cause embarrassment, affecting a patient's self-esteem, and may have a greater impact on quality of life (QoL) than the severity of the disease itself.[6] Thickened nails can also be painful, causing discomfort in walking and affecting other aspects of daily living.[3]

A number of underlying conditions, such as tinea pedis, nail damage, and nail psoriasis can contribute to risk as well as characteristics such as age and obesity. Underlying comorbidities, such as diabetes,[7,8] cancer,[7,9] immunodeficiency,[10] or peripheral arterial disease,[11] can increase susceptibility to onychomycosis.[7] An inherited genetic predisposition to infection has also been identified.[12]

Clinical trials provide guidance on likely treatment outcomes in these patients at risk. However, some comorbid conditions (i.e., peripheral vascular disease) can be exclusion criteria, many trials were not set up to specifically study certain comorbidities, and the demographics and disposition of patients who visit dermatology and podiatry practices can be very different from those enrolled in clinical trials.

Recently, a number of *post hoc* analyses have been published on the use of efinaconazole topical solution, 10%, in the treatment of mild-to-moderate onychomycosis. Where data exist, it is the authors' intention to review the findings in terms of the implications for successful treatment outcomes. In addition, they present new data with efinaconazole in terms of age and obesity.

Aging is the most common risk factor for onychomycosis,

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most likely due to poor peripheral circulation, longer exposure to pathogenic fungi, repeated nail trauma, suboptimal immune function, and slower nail growth.[13] In addition, various medical conditions more common in the elderly increase the risk of comorbid onychomycosis. Surveys suggest that overall the incidence is much higher in adults than in children, afflicting 0.6 percent of children under the age of 18 years, approximately 10 to 20 percent of adults and 15 to 40 percent of elderly people.[14–16] However, prevalence rates do not necessarily correlate with consultations. Not all of the patients we see with onychomycosis are elderly. This could be attributed to the fact that onychomycosis may be considered a cosmetic problem by the younger patients who are more conscious of their appearance coming forward for therapy. The increased incidence in the younger population could also be due to their exposure to occupation-related trauma predisposing them to onychomycosis or the more common use of occlusive footwear.

PATIENT CHARACTERISTICS

Treatment of mild-to-moderate onychomycosis with efinaconazole topical solution, 10%, does not seem to be influenced by patient age. Although there was a trend of younger patients (<40 years of age) doing better, this was not significant (Figure 1). Complete cure rates ranged from 16.7 percent in those patients over 65 years of age, to 23.4 percent in the younger patients. In elderly onychomycosis patients, it is likely that other factors, such as whether they can actually reach their toenails or have the manual dexterity to apply a topical product, will influence utilization of this treatment.

Obesity, with a body mass index (BMI) of 30kg/m^2 or greater has significantly increased among the US population over the past 30 years.[17] Approximately 119 million Americans, nearly two thirds of the adult population, are either overweight or obese.[18] Despite being recognized as a major public health problem, little is known about its impact on onychomycosis prevalence or outcomes. Significant increases have been observed in the incidence of onychomycosis in obese inpatient clinic attendees examined dermatologically for the presence of disease compared to normal controls.[19] In a study of more than 1,000 patients randomly invited to have an additional examination of their feet, obesity (with vascular disease and diabetes) was one of the three most prevalent predisposing factors among patients found to have fungal nail disease.[20]

In the two pivotal studies, efinaconazole topical solution, 10%, appears to be less effective in patients who are overweight or obese, and differences between obese patients and those with "normal" BMIs were significant (P=0.05, Figure 2). Almost three out of four patients (73.5%) with onychomycosis in the studies were either overweight (39.1%) or obese (34.4%). Complete cure rates at Week 52 ranged from 15.9 percent in the obese patients to 22.0 percent in patients who had a normal BMI. Other *post hoc* analyses have shown that female patients do

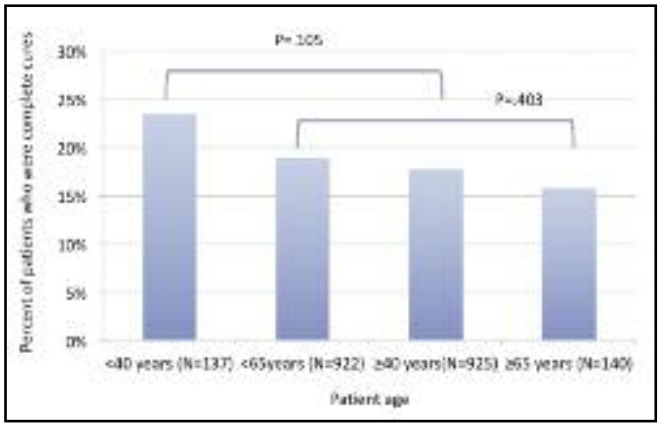

Figure 1. Influence of age on complete cure rates with efinaconazole at Week 52 (ITT subjects, pooled observed case data)

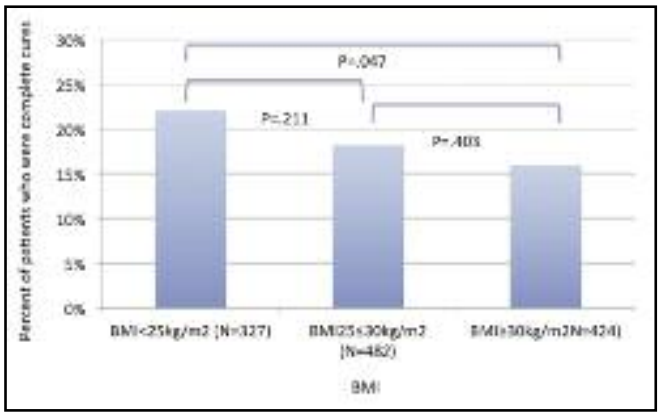

Figure 2. Influence of obesity on complete cure rates with efinaconazole at Week 52 (ITT subjects, pooled observed case data)

significantly better when treated with efinaconazole, compared to the males enrolled in the studies.[21] Although the reasons are not clear, this observation may have some impact on complete cure rates in the cohort with a BMI of <25kg/m^2; however, there was a greater proportion of males in the overweight group (84.6%) compared to those classified as obese (76.9%). Reasons why efinaconazole may be less effective in obese onychomycosis patients is less clear. Comorbid conditions could be a confounder; also, it is possible their disease could be more severe. Adherence may be impacted through some obese patients having difficulty reaching their feet to apply a topical treatment, or overall nail cleanliness may be compromised in obese patients who have difficulty showering. There was no significant difference in terms of age across the three groups, with the obese patients being the youngest (mean age 50.8 years). Given both the increasing prevalence of onychomycosis and the rise in obesity, this under-researched area warrants further investigation.

UNDERLYING CONDITIONS

The need to evaluate and treat onychomycosis and coexisting tinea pedis is critical if the long-term

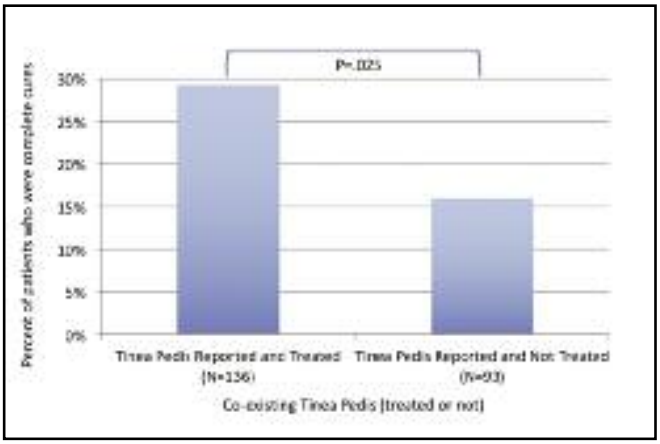

Figure 3. Influence of tinea pedis and its treatment on-study on complete cure rates with efinaconazole at Week 52 (ITT subjects, pooled observed case data)

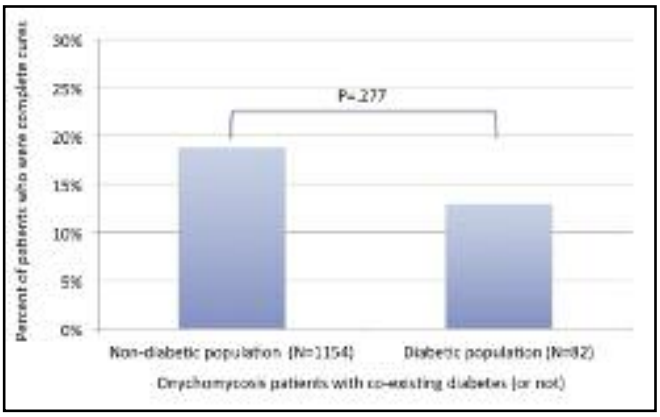

Figure 4. Influence of co-existing diabetes on complete cure rates with efinaconazole at Week 52 (ITT subjects, pooled observed case data)

management of onychomycosis is to be successful and the risk of recurrence or re-infection minimized. Onychomycosis has been found to be significantly more likely to be diagnosed in the context of tinea pedis ($P<0.001$);[22] a history of tinea pedis more than doubles the onychomycosis risk.[9] Interdigital tinea pedis (the most common subtype noted) was reported to coexist in 22.1 percent of onychomycosis patients in a large patient survey.[2] Finding the two diseases in the same patient is more common in men and noted in more than 1 in 4 elderly patients.[23]

A *post hoc* analysis of the efinaconazole studies of those patients where both diseases co-existed has recently been reported.[24] Interdigital tinea pedis was reported in 21.3 percent of patients on-study, a similar level to that recorded in previous surveys.[2] In efinaconazole-treated onychomycosis patients where coexisting tinea pedis was also treated on-study (with the physician's preferred treatment), complete cure rates (29.4%) were almost twice those when coexisting tinea pedis was not treated (16.1%, $P=0.025$, Figure 3). This important area also warrants further study with a larger cohort of patients.

UNDERLYING COMORBIDITIES

Diabetes is a very important comorbidity in onychomycosis patients. Almost a third of patients with diabetes suffer with onychomycosis,[25] and it is a significant limb-threatening infection if left untreated.[26] Patients who are human immunodeficiency virus (HIV) positive are also predisposed to the development of infections including onychomycosis and tinea pedis. Onychomycosis has been found in 1 in 4 HIV-positive individuals.[27] The impact of vascular abnormalities on the prevalence of onychomycosis is less clear. A recent study demonstrated a significant relationship between onychomycosis and venous insufficiency, but not peripheral artery disease.[28] It has been suggested that peripheral artery disease might be an independent predictor of onychomycosis,[29] and more recently in a small study that onychomycosis might act as an independent predictor of peripheral artery disease risk.[11]

Despite the importance of diabetes as an underlying comorbidity, few studies have looked at the treatment of onychomycosis in a diabetic population.[30] It has been suggested that people with diabetes who have onychomycosis may be more resistant to treatment due to hyperglycemia or poor foot hygiene.[31] Although the number of patients with coexisting diabetes in the efinaconazole studies was relatively small, it was still the largest cohort of diabetic patients with onychomycosis reported to date and supported earlier studies that had suggested similar efficacy in both cohorts.[32] Complete cure rates in the diabetic patients with onychomycosis were 13.0 percent compared with 18.8 percent in the nondiabetic population, although differences were not significant (Figure 4).[32]

CONCLUDING REMARKS

A number of underlying conditions, characteristics, and comorbidities can lead to an increased risk of onychomycosis, and yet clinical data in these patients are lacking.

The authors' review suggests that two patient characteristics can influence the efficacy of efinaconazole, namely gender[21] and obesity. In females, more than 27 percent of patients were complete cures at Week 52 with efinaconazole ($P=0.001$ versus the male population).[21] The reasons are not clear; male patients may have generally more severe disease, thicker toenails, or are less adherent. It may be that male patients just require a longer treatment course. There may be differences between the US and Japanese male populations in the two pivotal studies, as shorter people tend to have shorter toenails that would take less time to grow out, although these subpopulations have not been studied. Our data are the first to report treatment differences in onychomycosis patients relating to their BMI levels. Complete cure rate in those patients with a normal BMI was 22 percent, but again reasons why efinaconazole may be less effective in obese onychomycosis patients are not clear.

The presence of coexisting tinea pedis in an onychomycosis population is an important consideration for an effective treatment strategy. The need to diagnose and treat coexisting tinea pedis is well-recognized, but the data reviewed here are the first to show the significance in terms of patient outcomes. In those onychomycosis patients who had coexisting tinea pedis treated on-study, the complete cure rate was 29.4 percent.

Data in onychomycosis patients with underlying comorbidites are limited, in some cases because of exclusion criteria within clinical trial programs. To the authors' knowledge no, studies have specifically looked at treatment outcomes in diabetic patients with onychomycosis, or those onychomycosis patients suffering from HIV or peripheral artery disease. Data reviewed here in the subpopulation of diabetic patients with onychomycosis treated with efinaconazole supports other small subpopulations suggesting that in this important group, complete cure rates are statistically comparable to a normal onychomycosis population.

New topical agents for onychomycosis are now available (i.e., efinaconazole and tavaborole). Efinaconazole topical solution, 10%, has been shown to be effective in mild-to-moderate onychomycosis.[33] Data on tavaborole remains unpublished, but it is hoped they will provide additional insights into treating this important disease.

Large clinical trials can afford us the opportunity through *post hoc* analyses to provide important insights into the management of onychomycosis, but there are limitations, and trials that look specifically at the impact of risk factors and longer term treatment outcomes are needed. Onychomycosis remains a common, progressive and difficult disease to manage successfully, and one where early diagnosis and treatment is important irrespective of risk factors or comorbidities.

Data the authors have been able to review from previous *post hoc* analyses, and new data presented here on age and obesity, support the view that efinaconazole topical solution, 10%, should provide a useful option in the treatment of mild-to-moderate onychomycosis, particularly in female patients.

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