Safety and Efficacy of Oral Terbinafine in the Treatment of Onychomycosis: Analysis of the Elderly Subgroup in Improving Results in ONychomycosis-Concomitant Lamisil®* And Debridement (IRON-CLAD*), an Open-Label, Randomized Trial

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ABSTRACT

Objectives: The primary objective of this subanalysis was to examine the safety, tolerability, and efficacy of terbinafine in the treatment of toenail onychomycosis in the patients aged ≥65 years in the Improving Results in Onychomycosis Concomitant Lamisil® And Debridement (IRON-CLAD) trial. (Lamisil and IRON-CLAD are trademarks of Novartis Pharmaceuticals Corporation, East Hanover, New Jersey.) The secondary objective was to determine if toenail debridement would provide additional efficacy benefits in this subgroup.

Methods: The IRON-CLAD trial was an open-label, randomized, multicenter study of adults who underwent 4 weeks of screening and received terbinafine 250 mg/d for 12 weeks with or without aggressive toenail debridement (at baseline and weeks 6, 12, and 24). Clinic visits occurred at weeks 6, 12, 24, and 48. Safety and tolerability were assessed by adverse event (AE) rates based on changes in laboratory values, patient-volunteered information, answers to investigator questions, and physical examinations. Efficacy was evaluated by mycologic cure (negative microscopy of potassium hydroxide samples and negative culture), clinical cure (≥87.5% nail clearing), and complete cure (mycologic cure and complete toenail clearing) at week 48. The present subanalysis of IRON-CLAD results assessed participants aged ≥65 years (older subgroup).

Results: A total of 504 patients were randomized, of whom 75 were aged ≥65 years. In the older subgroup, the mean (SD) age was 68.9 (3.04), 86.7% (65/75) were white, and 66.7% (50/75) were male. Incidence of AEs reported during the treatment period or within 30 days after treatment discontinuation (treatment-emergent AEs [TEAEs]) was 28.0% in the older subgroup and 23.0% in the overall study population. Most TEAEs were mild (73.7%) to moderate (23.7%) in severity, and most (86.8%) were not suspected by the investigators to be related to study treatment. The most frequently occurring TEAEs in the older subgroup were nausea (4.0%), sinusitis (4.0%), arthralgia (2.7%), and hypercholesterolemia (2.7%). The proportion of participants who withdrew from the trial due to TEAEs was 4.0% (3/75) in the older group and 2.8% (14/504) in the overall population. Only 3 of 11 discontinuations in the older subgroup were due to a TEAE suspected by the investigator to be related to study treatment. Sixty-four percent of the older subgroup took antihypertensive medications, 25% took antidiabetics, and 47% took antilipemic medications. There were no clinical signs of drug interactions in the older subgroup. Clinical efficacy outcomes in the older subgroup were generally good and appeared to be comparable with those in the younger subgroup. At week 48, mycologic cure had occurred in 64.0% (95% CI, 53.1%–74.9%) of the older subgroup, clinical cure in 41.3% (95% CI, 30.2%–52.5%), and complete cure in 28.0% (95% CI, 17.8%–38.2%). Debridement did not appear to affect mycologic outcomes or clinical effectiveness, but rates of clinical and complete cure appeared to be higher among older patients who underwent adjuvant debridement.

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Accepted for publication November 22, 2005.
doi:10.1016/j.amjopharm.2005.12.012

1543-5946/06/$19.00

Conclusions: The results of this subanalysis suggest that terbinafine was well tolerated and efficacious in these patients aged ≥65 years with moderate to severe toenail onychomycosis, many of whom were taking antihypertensives, antidiabetics, or lipid-lowering agents concomitantly. There were no reported clinical signs of drug interactions. (*Am J Geriatr Pharmacother.* 2006;4:1–13)

Key words: elderly, antifungal, terbinafine, onychomycosis, safety, tolerability, efficacy.

INTRODUCTION

Onychomycosis, a common fungal infection of the nail,[1] affects an estimated 8% to 14% of the US population.[2,3] It is prevalent in older individuals,[1,4] who often have more severe disease and are at greater risk for complications than younger people.[5,6] Typically, the affected nails are visibly abnormal, leading to embarrassment and negative effects on patients' personal, social, and occupational functioning.[7,8]

The management of onychomycosis has greatly improved with the marketing approval by the US Food and Drug Administration (FDA) of the newer oral antifungal agents terbinafine and itraconazole, as well as topical ciclopirox nail lacquer. Prescribing information for these 3 drugs reports complete cure (100% nail clearing and mycologic cure) rates of 38% for terbinafine,[9] 14% for itraconazole,[10] and 5.5% to 8.5% for topical ciclopirox.[11] Thus, oral antifungal agents are the most effective available treatment options for onychomycosis.[8] However, they may be used sparingly in older patients due to the perception that such patients may be at higher risk for drug interactions and adverse events (AEs) because of age-related physiologic changes and the use of concomitant medications to treat various chronic conditions.[5,12,13] When treating onychomycosis in older patients, physicians may be averse to adding another drug to the long list of concomitant medications taken for comorbidities. Understandably, there is a concern about the risk of drug interactions in older patients taking multiple medications. As a result, these patients may not receive appropriate therapy.

Terbinafine, a synthetic allylamine antifungal agent, was first approved for the management of onychomycosis in the United Kingdom in 1991 and in the United States in May 1996, and has since been used effectively to treat onychomycosis in adults and special patient populations.[4] This broad-spectrum allylamine is fungicidal in vitro, whereas the azoles (eg, itraconazole) are primarily fungistatic. This may partially account for the greater efficacy of terbinafine.[14]

In a prospective, randomized, double-blind, double-dummy, multicenter, parallel-group study of terbinafine 250 mg/d for 12 or 16 weeks versus itraconazole 400 mg/d for 1 week in every 4 weeks for 12 or 16 weeks,[14] the rates of clinical, mycologic, and complete cure at 72 weeks, respectively, of toenail onychomycosis were 53.6% (59/110), 75.7% (81/107), and 45.8% (49/107), respectively, with 12 weeks of treatment and 60.2% (59/98), 80.8% (80/99), and 55.1% (54/98), respectively, with 16 weeks of terbinafine. With itraconazole, the rates of clinical, mycologic, and complete cure at 72 weeks were 31.8% (34/107), 38.3% (41/107), and 23.4% (25/107), respectively, with 12 weeks of treatment and 32.1% (35/109), 49.1% (53/108), and 25.9% (28/108), respectively, with 16 weeks of treatment. The differences between terbinafine and itraconazole were statistically significant for clinical cure ($P < 0.003$), mycologic cure ($P < 0.001$), and complete cure ($P < 0.005$). Patients participating in this study were later followed in long-term extension studies in Finland[15] and Iceland[16] for 4 and 5 years, respectively, and results showed that nearly 50% remained mycologically cured after nearly 5 years.[16] A meta-analysis reported mean (SE) rates of 76% (3%) for mycologic cure (defined as negative microscopy and negative culture in the meta-analysis) and 66% (5%) for clinical response (defined as nail visibly clear of infection or marked improvement) among 15 randomized clinical trials reporting these variables.[17]

Terbinafine does not inhibit cytochrome P450 (CYP) 3A4, a major drug metabolizer,[18,19] and is metabolized in the liver by at least 7 other CYP isozymes, including 1A2, 3A4, 3A5, 2B6, 2C8, 2C9, and 2C19.[19] Therefore, it would be expected to have a low propensity for interacting with common medications such as antilipemic agents (including statins), antihypertensives, and oral hypoglycemic agents.[20] Terbinafine is, however, an inhibitor of CYP2D6. Examples of drugs that are metabolized by CYP2D6 include older antidepressants (ie, amitriptyline, imipramine, nortriptyline); the selective serotonin reuptake inhibitors fluoxetine and paroxetine; citalopram; and some older β-blockers (ie, metoprolol, propranolol).[19–21]

However, except for 2 smaller studies,[13,22] there is a lack of recent clinical trial data on tolerability of oral terbinafine in older subjects. As in many infections that affect older populations, there is also a paucity of clinical data on efficacy of terbinafine in older patients relative to younger patients.