

**TO THE EDITOR**

I was greatly interested to read the article by Dr. Katz regarding managed care and onychomycosis.<sup>1</sup> I applaud Dr. Katz's efforts, as onychomycosis is a significant problem for many patients and should be respected as an infectious disorder that requires appropriate evaluation, and in many cases, therapeutic intervention. The major advance and most important part of the treatment of onychomycosis is using an effective oral antifungal agent. I do have some concerns with the article, mostly related to comparative perceptions between terbinafine and itraconazole.

Dr. Katz indicates that itraconazole "forms a fungistatic area and terbinafine forms a fungicidal barrier preventing invasion of dermatophytes into the nail." This description may not be pertinent clinically. In fact, the issue of "cidal versus static" is based on in vitro laboratory testing, the results of which vary significantly depending on the parameters and method of laboratory testing.<sup>2</sup> As stated in the terbinafine US product monograph, the clinical relevance of whether or not an agent is fungicidal has not been demonstrated. Clinical studies indicate that the major factors influencing efficacy are correct diagnosis and completion of appropriate dosage regimens. With regard to onychomycosis, oral agents appear to prevent proliferation of fungal organisms until the diseased plate is replaced by normal nail plate.

Secondly, the article does not adequately address the fact that the use of pulse itraconazole therapy is a recommended regimen for the treatment of both fingernail and toenail onychomycosis. Although pulse itraconazole has only been evaluated and approved in the United States by the Food and Drug Administration for fingernail disease<sup>3,4</sup> it is commonly used for toenail onychomycosis worldwide, including the United States. Current research recommends the use of continuous terbinafine therapy or pulse itraconazole therapy when treating dermatophyte onychomycosis.<sup>3-5</sup> Available data also indicates that pulse therapy with itraconazole is as or more effective than continuous itraconazole when treating onychomycosis and offers the additional advantages of reduced drug exposure and lower cost.<sup>4,6</sup>

Dr. Katz also indicates that in clinical trials with itraconazole continuous therapy, 4% of patients had elevated liver enzymes at or above twice the upper limit of normal range. Although he suggests that liver function testing should be performed periodically, he fails to address recommendations with oral terbinafine for liver function testing. The US product monographs suggest periodic liver function testing be completed with continuous itraconazole usage for more than 30 days and continuous terbinafine usage for more than 6 weeks. Physicians are encouraged to use their judgement and adjust liver function testing recommendations appropriately in patients with pre-existing liver disease. In addition, complete blood cell count (CBC) testing is

suggested in the US product monograph with oral terbinafine when used in immuno-compromised patients. Some physicians perform routine CBC testing in all patients due to uncommon, yet sporadically reported significant blood dyscrasias reported with the use of oral terbinafine.<sup>5,7,8</sup> The bottom line is that laboratory monitoring recommendations may be adjusted on a case-by-case basis suited to the comfort level of the physician prescribing these agents. Fortunately hepatotoxicity with both agents and blood dyscrasias with oral terbinafine have been rare. Physicians are nevertheless encouraged to develop rational monitoring guidelines.

In summary, both oral itraconazole and terbinafine represent major advances in the treatment of toenail onychomycosis. In patients significantly affected by this infectious disorder, an attempt to achieve a maximum benefit with the use of oral therapy combined with adjunctive modalities offers the most cost-effective approach.

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**IN REPLY**

I agree with Dr. Del Rosso that since the introduction of itraconazole and terbinafine the paradigms for treating onychomycosis have dramatically changed and that practitioners should attempt to achieve the maximum

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benefit with the use of oral antifungal therapy. In the United States, both drugs are approved as safe and effective for this relatively common disorder. Furthermore, the majority of patients treated with either drug have an uneventful course. Serious adverse experiences are very rare. However, his letter does raise several points that I am happy to address and confirm.

First, Dr. Del Rosso questions the clinical significance of in vitro laboratory studies that indicate fungicidal versus fungistatic antifungal activity of a drug.<sup>1</sup> Furthermore, he suggests that clinical correlates rather than the "cidal" or "static" attributes of a drug may affect the efficacy of an oral antifungal. He cites making the correct diagnosis, patient compliance using appropriate dosing regimens, and regrowth of a normal nail as the major clinical correlates. While these clinical correlates are indeed important, in the case of itraconazole versus terbinafine differences in in vivo cure rates suggest that the in vitro inherent fungicidal or fungistatic antifungal activity between the drugs may be more important.<sup>2-4</sup> In order to develop this point, I would like to review 2 recent well-controlled, large-scale "toe to toe" comparative trials.

De Backer et al<sup>5</sup> performed a randomized, double-blind study comparing the outcomes at 48 weeks following 12 weeks of continuous daily oral treatment with terbinafine (250 mg/day) or daily itraconazole (200 mg/day) in 372 patients. At week 48, negative mycology was found in 73% of those treated with terbinafine and 46% treated with itraconazole ( $P < 0.0001$ ). Clinical cure or only minimal symptoms were found in 76% of those treated with terbinafine vs 58% for those treated with itraconazole ( $P = 0.001$ ). The second study was a randomized, double-dummy, multinational study,<sup>6</sup> comparing the results of 4 treatment groups at the end of 72 weeks for either daily terbinafine 250 mg ( $T_{12} = 3$  months,  $T_{16} = 4$  months) versus intermittent itraconazole 400 mg/day x 7 days per pulse for 1 week out of a month ( $I_3 = 3$  pulses,  $I_4 = 4$  pulses) in 496 patients. At the end of 72 weeks daily terbinafine ( $P < 0.0001$ ) had more mycological cures ( $T_{12} = 76\%$ ,  $T_{16} = 81\%$ ) than pulsed itraconazole ( $I_3 = 38\%$ ,  $I_4 = 49\%$ ). Complete clinical cure (normal nail) was also statistically significant ( $P < 0.002$ ) in favor of terbinafine ( $T_{12} = 54\%$ ,  $T_{16} = 60\%$ ) versus pulsed itraconazole ( $I_3 = 32\%$ ,  $I_4 = 32\%$ ). These studies of patients with confirmed diagnoses of onychomycosis had evenly matched cohorts of compliant patients treated with either approved or experimental dosing regimens ("pulse dosing"). Both studies indicate that daily terbinafine had significantly higher cures (mycological and normal appearing nails) than itraconazole (daily or intermittently) and provides

a clinical correlate for terbinafine in vitro fungicidal activity.

Second, to my knowledge, the current approved dosing schedules for itraconazole and terbinafine are accurate as stated in the article.<sup>7,8</sup> As Dr. Del Rosso points out, intermittent pulse dosing of itraconazole for toenail onychomycosis is not an approved dosing regimen in the United States.

Finally, among clinicians, laboratory studies prior to and during treatment with either itraconazole or terbinafine are controversial. There are those that obtain a complete blood count and liver and renal function tests before and during courses of treatment and those who do not. As stated in the article, I believe that during the selection of therapy, baseline hematological and serum chemistry screenings are recommended before starting systemic antifungal therapy. Furthermore, follow up laboratory studies are recommended as outlined in the product monograph for the agent selected.<sup>7,8</sup>

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