Onychomycosis: Improved Cure Rates with Itraconazole and Terbinafine.

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Editors' Note: *This month we continue the new feature - STEPped Care: An Evidence-Based Approach to Drug Therapy. These articles are designed to provide concise answers to the drug therapy questions that family physicians encounter in their daily practice. The format of the feature will follow the mnemonic STEP: safety (an analysis of adverse effects that patients and providers care about), tolerability (pooled dropout rates from large clinical trials), effectiveness (how well the drugs work and in what patient population[s]), and price (costs of drug, but also cost effectiveness of therapy).*[1] *Hence, the name STEPped Care. Since the informatics pioneers at McMaster University introduced evidence-based medicine,*[2] *Slawson and colleagues*[3,4] *have brought it to mainstream family medicine education and practice. This feature is designed to further the mission of searching for the truth in medical practice. Authors will provide information in a structured format that allows the readers to get to the meat of a therapeutic issue in a way that can help physicians (and patients) make informed decisions. The articles will discourage the use of disease-oriented evidence (DOE) to make treatment decisions. Examples of DOEs include blood pressure lowering, decreases in hemoglobin A_{1c} and so on. We will include studies that are POEMs - patient-oriented evidence that matters (myocardial infarctions, pain, strokes, mortality, etc) - with the goal of offering our patients the most practical, appropriate, and scientifically substantiated therapies. Number needed to treat to observe benefit in a single patient will also be included as a way of defining advantages in terms that are relatively easy to understand.*[5,6]

At times this effort will be frustrating. Even as vast as the biomedical literature is, it does not always support what clinicians do. We will avoid making conclusions that are not supported by POEMs. Nevertheless, POEMs should be incorporated into clinical practice. The rest is up to the reader. Blending POEMs with rational thought, clinical experience, and importantly, patient preferences can be the essence of the art of medicine.

We hope you will find these new articles useful and easy to read. Your comments and suggestions are welcome. You may contact the editors through the editorial office of JABFP or on the Internet (http://clinic.isu.edu/drugsteps/intro.html). We hope the articles provide you with useful information that can be applied in everyday practice, and we look forward to your feedback.

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Onychomycosis is a common fungal infection of the nails with a prevalence among adults of 2% to 4%.[1,2] Dermatophytes represent the principal causative agents of onychomycosis, and for years it was thought that the condition was incurable.[3] Topical agents have been ineffective, and the available oral agents require prolonged therapy and are associ-

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ated with frequent recurrences of infection and common adverse effects. The efficacy of the antifungal agent griseofulvin (GrifulvinV, Grisactin, Gris-PEG) is limited because of its irregular absorption and its need for long duration of therapy (up to 24 months). Although ketoconazole (Nizoral) has been somewhat effective, the risk for hepatotoxicity, along with its potential for drug interactions, limits its use.[2]

Fortunately, within the past decade the development of the newer systemic antimycotics—itraconazole (Sporanox), terbinafine (Lamisil), and fluconazole (Diflucan)—has led to higher cure rates for onychomycosis.[1–3] Itraconazole is an orally active triazole derivative that exerts its antifungal activity by inhibiting the enzyme 14-α-demethylase and thus impairing the synthesis of ergosterol in the fungal cell membrane. Terbinafine is an orally active allylamine that also inhibits the synthesis of ergosterol. In contrast to itraconazole, terbinafine disrupts the fungal cell membrane by inhibiting the enzyme squalene epoxidase. Fluconazole is also an orally active triazole; however, it has not been sufficiently evaluated in onychomycosis and is not approved for that condition. Consequently, treatment within this review will focus on comparative trials of itraconazole and terbinafine.

Methods

MEDLINE was searched from January 1985 to September 1999 using the search terms "onychomycosis," "antifungal agents," "cure rates," "quality of life," "diabetes mellitus," "HIV infections," and "cost-effectiveness." The search for treatment references was limited to comparative trials of itraconazole and terbinafine in humans published in the English language. Studies were selected if they had mycologic cure rates as primary outcomes, or if they contained patient-oriented evidence that matters (POEMs) as outcomes, including clinical cure rates, quality-of-life data, or cost-effectiveness data. For completeness other references involving the pharmacokinetics and pharmacology of antifungal agents in onychomycosis were included at the discretion of the authors. This review investigates the use of itraconazole and terbinafine in onychomycosis by using the STEP approach: *s*afety (an analysis of adverse effects with which patients and providers are concerned), *t*olerability (dropout rates from comparative trials), *e*ffectiveness (how well the drugs work), and *p*rice (cost of drug and cost-effectiveness of therapy).

Selection of Trials

Itraconazole and terbinafine have been shown in separate trials to be effective when compared with placebo, as well as other antifungal medications, in the treatment of onychomycosis.[4–6]

Subsequent studies have focused on head-to-head comparisons of terbinafine and itraconazole. For this review we selected six trials comparing terbinafine with itraconazole. Four studies compared daily oral therapy for 12 weeks with terbinafine and itraconazole.[2,3,7,8] One study compared intermittent terbinafine therapy with intermittent itraconazole therapy and continuous terbinafine therapy,[9] and one large study compared daily terbinafine therapy with itraconazole pulse therapy.[1]

Eight additional trials containing other POEMs were also included. Five of these trials focused on quality-of-life issues in onychomycosis, two trials evaluated onychomycosis in special populations, and one trial was a cost-effectiveness study.

Safety and Tolerability

Both itraconazole and terbinafine were generally safe and well tolerated in the selected comparative trials.[1–3,7,8] None of the comparative trials discovered adverse effects not previously reported with the agents. The most common adverse events with terbinafine included gastrointestinal symptoms (diarrhea, dyspepsia, abdominal pain), liver test abnormalities, rash, urticaria, pruritus, and taste disturbances. For itraconazole the most common adverse effects included gastrointestinal symptoms (nausea, vomiting, diarrhea, abdominal pain), edema, rash, headache, and liver test abnormalities.[1–3,7,8]

In the trial by Degreef et al,[8] 2 patients receiving itraconazole therapy and 11 receiving terbinafine therapy (1.4% vs 7.6%, respectively) discontinued treatment because of events thought to be directly related to the study medication. One patient in the terbinafine group discontinued treatment because of abnormal liver function tests. In addition, 22% of patients receiving itraconazole and 33% of patients receiving terbinafine reported other mild adverse events. In the trial by Brautigam et al,[2] treatment was discontinued in 3 patients (3.2%) receiving terbinafine and 4 patients (4.1%) receiving itraconazole. One patient in each group discon-

tinued treatment because of serious liver function abnormalities. One patient in the itraconazole group dropped out because of paresthesias, and the other 4 patients withdrew because of gastrointestinal complaints. In addition, 38 patients (40%) receiving terbinafine and 47 patients (48%) receiving itraconazole reported other minor adverse events. Participating dermatologists assessed the tolerability of both groups as excellent in 93% of patients.

In the trial by De Backer et al,[7] both drugs were reported to be well tolerated by 90% of patients, and no specific details were given regarding adverse events. In the trial by Arenas et al,[3] the rate of adverse events was reported to be 47% in the terbinafine group and 21% in the itraconazole group. Of these 43 patients, 3 (11.1%) in the itraconazole group dropped out for unknown reasons, and 1 (3.7%) dropped out because of headache. In the terbinafine group 7 patients (25.9%) dropped out for unknown reasons, and 2 patients (7.7%) dropped out for other adverse events (abdominal pain and rash). In the trial by Tosti et al[9] minor drug-related events were reported in 2 patients (3.3%) taking terbinafine; no adverse effects were reported with itraconazole. Also, no abnormal laboratory parameters were noted with either drug. In the Evans and Sigurgeirsson trial,[1] 116 patients (47.5%) reported adverse events in the terbinafine group and 120 patients (47.6%) reported adverse events in the itraconazole group. In this trial, 21 patients (8.6%) in the terbinafine groups and 13 patients (5.2%) in the itraconazole group withdrew because of adverse effects. The authors concluded there were no significant differences in adverse events among the treatment regimens.

Drug interactions were not evaluated in any of the comparative trials; however, both medications will interact with other agents. Both itraconazole and terbinafine are metabolized extensively in the liver and are affected by inducers and inhibitors of the cytochrome P-450 system. Terbinafine appears to have less potential for drug interactions; even so, caution should be exercised with both medications, especially for patients receiving concomitant agents that induce or inhibit the cytochrome-P-450 system. A partial list of drugs that can interact with terbinafine and itraconazole appears in Table 1.

Table 1. Potential Drug Interactions with Itraconazole and Terbinafine.

Itraconazole (Cytochrome P-450 3A4)	Terbinafine (Cytochrome P-450 2C19 and 2D6)
Cisapride	Cimetidine
Cyclosporine	Cyclosporine
Digoxin	Rifampin
H_2 antagonists	Warfarin
Oral hypoglycemics	
Phenytoin, phenobarbital, carbamazepine	
Rifampin	
Ritonavir, indinavir	
Simvastatin, lovastatin	
Terfenadine, astemizole	
Warfarin	

Effectiveness

Arenas et al,[3] in an open, randomized study funded by Janssen Pharmaceutica, compared itraconazole 200 mg once daily for 12 weeks with terbinafine 250 mg once daily for 12 weeks. Fifty-three patients began the study, and 43 were evaluated at a final follow-up 6 months after completing therapy. Parameters compared at the follow-up evaluation were fungal smears, fungal cultures, affected nail area, and medical evaluation of therapy. Only 1 patient (5.6%) in the terbinafine group had a positive culture after treatment, and 1 patient (4.3%) in the itraconazole group had a positive smear. The authors did not detect any statistically significant differences between itraconazole and terbinafine therapy in any of the outcome measures. The authors, however, failed to report the power of their study to detect a predetermined difference.

In a randomized, double-blind trial funded by Sandoz (now Novartis Pharmaceuticals), Brautigam et al[2] also compared daily terbinafine 250 mg with itraconazole 200 mg. They entered 195 patients in the study, of which 25 withdrew before final follow-up at 10 months after completion of 12 weeks of therapy. The authors reported negative culture rates of 81% for the terbinafine group and 63% for the itraconazole group. Measurements of unaffected toenail length resulted in a mean of 9.4 mm in the terbinafine group and 7.9 mm in the itraconazole group. These results were reported as statistically significant. The authors concluded that terbinafine was more effective than itraconazole.

De Backer et al[7] reported the results of a randomized, double-blind intention-to-treat trial funded by Sandoz. They compared itraconazole 200 mg/d with terbinafine 250 mg/d. A total of 372

patients began the 12 weeks of therapy, but no dropout rate was reported. After 4 months of therapy, fungal cultures, measurement of unaffected nail length, and a clinical scoring system were completed. Negative culture rates were 45.8% for itraconazole and 73% for terbinafine. The mean unaffected toenail length was 7.7 mm for itraconazole and 9.1 mm for terbinafine. The clinical scoring system of symptoms favored terbinafine compared with itraconazole (76.3% vs 58.1%, respectively). All differences were reported as statistically significant.

Tosti et al[9] reported the results of an open, randomized trial comparing intermittent terbinafine therapy with continuous terbinafine therapy and intermittent itraconazole therapy. This small trial consisted of 63 patients who were randomized to receive terbinafine 250 mg daily for 12 weeks, terbinafine 500 mg daily for 1 week every month for 4 months, or itraconazole 400 mg daily for 1 week every month for 4 months. Mycologic cure rates at the end of follow-up were 94.1% for continuous terbinafine therapy, 80% for intermittent terbinafine therapy, and 75% for intermittent itraconazole therapy. Statistical analysis, however, did not show any significant differences among the three regimens. The results suggested a trend in favor of continuous terbinafine when compared with intermittent terbinafine and showed that intermittent itraconazole and intermittent terbinafine have similar efficacy.

Evans and Sigurgeirsson[1] reported the results of a trial comparing daily terbinafine therapy with pulse dose itraconazole therapy. This well-designed, randomized, double-blind study included intention-to-treat analysis, but the published article reported results only for those completing follow-up. Of 506 patients at initiation of therapy, 409 completed the study follow-up at 72 weeks. There were two terbinafine treatment arms, 250 mg daily for 12 and 16 weeks, and two itraconazole arms, 400 mg daily for 1 week each month for 3 and 4 months. At follow-up the terbinafine groups had better outcomes than the itraconazole groups for both negative culture rates (76%–81% vs 38%–49%) and clinical cures (54%–60% vs 32%). Results were reported as significant and supported the authors' conclusion that daily therapy with terbinafine was superior to pulse dose therapy with itraconazole.

Degreef et al[8] reported the results of a multicenter, randomized, double-blind, intention-to-treat trial comparing daily itraconazole with terbinafine. This well-designed study had 292 patients at initiation of therapy and had adequate data on 289 patients for analysis. At the end of 3 months' follow-up, clinical cure rates were 42.8% and 38.9% for itraconazole and terbinafine, respectively. On an intention-to-treat basis, mycologic cure rates were 54% in the itraconazole group compared with 56% for the terbinafine group. Statistically these results were reported as being significantly equivalent.

In addition to mycologic and clinical cures, there are other POEMs to consider in onychomycosis. Special patient populations are often affected, specifically diabetic patients and HIV-positive patients. The general consensus is that onychomycosis is not more common among diabetic patients; however, the potential for serious sequelae is possibly greater.[10] In HIV-positive patients, onychomycosis is a common early sign of disease and is thus a visible sign that the patient's immune system is deteriorating. As a result, a diagnosis of onychomycosis could lead to greater emotional distress in this patient population.[11] No comparative studies of treatment have been completed in these special populations.

Several studies have been conducted to determine how onychomycosis affects a patient's quality of life.[12–16] Lubeck et al[12] first reported the impact of onychomycosis on quality of life in 1993. In the analysis, 299 patients with onychomycosis and 381 control patients were interviewed by telephone. A quality-of-life survey was the instrument used, which included questions pertaining to patient-reported problems, concerns with physical appearance, and concerns with physical performance related to onychomycosis. When compared with the control group, onychomycosis patients scored lower in all but one category. Categories included general health, bodily pain, mental health, social functioning, and physical appearance. A total of 88% of patients also indicated they would take oral medications daily for 6 months, even if they had short-term side effects. This analysis was limited in that it excluded patients older than 60 years (a large population of those affected with onychomycosis), and it did not define how the diagnosis of onychomycosis was derived.

Table 2. Average Wholesale Price of Recommended Therapy with Itraconazole and Terbinafine.

Dose	Cost ($)
Terbinafine, 250 mg once daily for 12 weeks	612.72
Terbinafine pulse therapy, 500 mg once daily for 1 wk/mo for 4 months*	408.48
Itraconazole, 200 mg once daily for 12 weeks	1,141.84
Itraconazole pulse therapy, 400 mg once daily for 1 wk/mo for 4 months	761.52

From Drug Topics Red Book.[17]
*Pulse therapy with terbinafine has not been approved by the Food and Drug Administration; one small study suggests possible efficacy.[9]

Subsequent studies have reported similar results. Elewski[13] reported results from a survey of patients responding to a newspaper advertisement. A total of 93 patients completed the survey, and 92% of these patients reported experiencing negative effects on the quality-of-life indicators of the survey instrument (both physical and psychosocial components). In addition, 41% reported experiencing pain or discomfort as a result of onychomycosis. Schein et al[14] completed an observational study of 129 onychomycosis patients who were not currently receiving oral or systemic therapy. Again patients reported onychomycosis was a problem in their lives (mean quality-of-life score of 60 out of 100). Additionally, this study showed that women reported more problems caused by onychomycosis. Whittam and Hay[15] reported results from 60 onychomycosis patients in the United Kingdom. More than one third of patients reported pain or discomfort in their feet, which resulted in limitations of their activities. Five patients (8%) reported that pain in their feet or toes made their lives a misery. Drake et al[16] completed a telephone survey of 258 patients with onychomycosis. The results showed that 193 patients (75%) reported embarrassment about their nails, and 124 patients (48%) reported pain associated with their condition. A total of 249 patients (97%) reported they would be willing to pay out-of-pocket for antifungal therapy with an 80% cure rate.

These studies all suggest that onychomycosis has a negative impact on quality of life and that our patients often desire treatment. However, it is difficult to interpret and evaluate the validity of these studies, because no reference standard quality-of-life instrument exists for patients with onychomycosis.

Price

Onychomycosis also has a substantial economic impact on patients and health care in general. It has been estimated the cost of caring for Medicare patients with onychomycosis is more than $43 million per year.[16] These costs are associated with numerous visits to primary care providers, as well as podiatrists and dermatologists, in addition to ineffective treatments and recurrences. The costs of recommended therapy of itraconazole and terbinafine are listed in Table 2.[17]

Bootman[18] completed a cost-effectiveness study of itraconazole and terbinafine based on the two comparative trials by Brautigam et al[2] and De Backer et al.[7] The cost-effective analysis included drug-acquisition costs, the costs of medical management, and costs associated with adverse drug reactions for both itraconazole and terbinafine. Total cost of itraconazole treatment (200 mg once a day for 12 weeks) was $1,216.40–$1,218.80 compared with $697.55–$699.11 with terbinafine (250 mg once a day for 12 weeks). Bootman concluded that terbinafine was more cost-effective in treating onychomycosis.

Table 3. Drug STEPs Overview.

Safety and tolerability	Itraconazole and terbinafine are safe and well tolerated and have been evaluated in placebo-controlled and comparative trials
Effectiveness	Itraconazole and terbinafine are similarly effective in improving mycologic and clinical cure rates when comparing terbinafine 250 mg once daily for 12 weeks with itraconazole 200 mg once daily for 12 weeks.
	Terbinafine 250 mg once daily for 12 weeks is more effective than pulse dosing of itraconazole. Continuous terbinafine therapy tends to be more effective than intermittent terbinafine therapy, whereas intermittent itraconazole has an efficacy similar to that of intermittent terbinafine
Price	Cost of terbinafine therapy is $7/d for 12 weeks compared with $14/d for 12 weeks for itraconazole therapy. Intermittent therapy for 4 months with terbinafine is approximately $400 compared with approximately $750 for intermittent therapy with itraconazole
Summary	Itraconazole and terbinafine improve cure rates and potentially improve patients' quality of life

Summary

Onychomycosis is a disease that is important to our patients. Based on the current literature, recent developments of newer antifungal agents have improved cure rates of onychomycosis in the past few years (Table 3). No significant differences in safety and tolerability between itraconazole and terbinafine exist. Terbinafine does appear to have a preferable drug interaction profile. Daily therapy with either agent at standard doses has been shown to be effective when compared with placebo.[4] When studies have directly compared daily administration of terbinafine and itraconazole, both medications have shown similar efficacy. Daily terbinafine therapy, however, appears to be more effective than pulse therapy with itraconazole. In addition, one small study showed a trend in favor of continuous rather than intermittent terbinafine therapy and similar efficacy of intermittent itraconazole and intermittent terbinafine therapy. Furthermore, terbinafine is more cost-effective than itraconazole. Finally, as quality-of-life data suggest, onychomycosis is important to our patients and affects both physical and psychosocial components of our patients' lives.

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