Economic Analysis of Oral and Topical Therapies For Onychomycosis of the Toenails and Fingernails

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ABSTRACT

Objective: Several antifungal agents are indicated for onychomycosis, a fungal infection of the toenails and fingernails. These agents differ in their dosing regimen, efficacy, adverse events profile, potential for drug interaction, and cost. We conducted a pharmacoeconomic analysis of oral and topical therapies for onychomycosis from the perspective of a hypothetical managed care payer to determine the most cost-effective agent.

Design: A decision analytic model was developed to evaluate the pharmacoeconomic profiles of itraconazole–continuous (Sporanox, Janssen Pharmaceutica), itraconazole–pulse (Sporanox, Janssen Pharmaceutica), terbinafine (Lamisil, Novartis Pharmaceuticals), and ciclopirox (Penlac, Dermik Laboratories) in the treatment of fingernail and toenail onychomycosis.

Methodology: We conducted a meta-analysis of the available literature to populate the decision analytic model with clinical point estimates for success, failure, and relapse. A panel of expert dermatologists defined resources consumed during the onychomycosis treatment process. These resources were then assigned values, using publicly available data sources, to reflect the U.S. managed care perspective. These clinical and economic data elements were integrated in the decision analytic model to arrive at the expected cost of treatment for each drug. Additionally, incremental cost-effectiveness was calculated for treatment success and disease-free days achieved by each therapy. Finally, a policy-level analysis of the budgetary impact of using the therapies for onychomycosis in a managed care setting was conducted.

Results: The meta-analysis demonstrated terbinafine to be the therapeutic alternative with the highest success rate for both fingernails (96.55 percent) and toenails (81.15 percent). Terbinafine also had the lowest relapse rate (6.42 percent) and the highest number of disease-free days for both fingernails and toenails. Subsequently, in terms of cost-effectiveness, terbinafine dominated all other comparators for fingernails and toenails.

Conclusions: Based on the patient-level analysis, we concluded that terbinafine is the most cost-effective therapy in the treatment of onychomycosis from a managed care perspective. Furthermore, at the policy level, increased utilization of terbinafine among onychomycosis patients is likely to reduce the managed care organizations' per member per month cost.

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INTRODUCTION

Onychomycosis is a fungal infection of the toenails and fingernails, with the former more commonly affected. Dermatophytes, such as those of the genera *Epidermophton*, *Microsporum*, and *Trichophyton*, are estimated to be involved in up to 95 percent of onychomycosis infections (Summerbell 1989). Nondermatophyte origins are less common and include molds and yeasts, such as *Candida albicans*.

Onychomycosis generally affects men and women in equal proportions, with estimates of overall prevalence reported in the literature varying widely, from 2.6 percent (Sais 1995) to 13.4 percent (Elewski 1997a). The prevalence is much higher in certain populations, such as the elderly and those with immunosuppressive conditions (Levy 1997). This disease can result in permanent nail deformity and can be a source of embarrassment and reduced self-esteem for the infected patient (Drake 1995, Lubeck 1993, Schein 1997).

The rationale for treating onychomycosis goes far beyond patients' cosmetic complaints, however. Toenail onychomycosis takes many months to control and, during this time, causes pain and can make walking difficult. Therefore, onychomycosis treatment is necessary to overcome physical limitations, reduce the spread of infections, and reduce pain.

Some populations are at higher risk for developing more serious complications due to the disease. For example, diabetes patients are at a threefold higher risk of secondary infection, gangrene, and foot ulcers, compared with diabetes patients without onychomycosis (Boyko 1999). Immunocompromised patients can develop widespread cutaneous infections that are resistant to topical therapy (Radentz 1989). Clinical success also is affected by the location of the infection, in that fingernail infections are usually cured more easily and quickly than toenail infections (Goldfarb 1960).

Newer agents like ciclopirox (Penlac) have been added as therapeutic choices for onychomycosis. Although onychomycosis treatment with oral antifungal agents is associated with elevated drug costs, oral treatment stands above other alternatives on the basis of its higher mycological and clinical cure rates (Brautigam 1996, Tom 1999, Gupta 1998, Evans 1999). In a study comparing oral and topical therapies through 9-months of clinical care, toenail treatment using oral agents generated higher costs when compared with treatment using topical agents (Stier 2001). Nevertheless, the cost of oral antifungal treatment is outweighed by its increased clinical effectiveness, lower toxicity, and reduced treatment time (Ling 1998, Scher 1998).

Several economic analyses have been published examining oral and topical antifungal agents in the treatment of onychomycosis (Marchetti 1996, Arkian 1994, Einarson 1994, Einarson 1995b, Davis 1995, Gupta 2000a, Joish 2001). These studies relied on similar model structures and data from clinical trials. Recently, more information has been published on the efficacy of these drugs and newer drugs that have become available in the treatment of onychomycosis; these efficacy data have been included in the present analysis.

To assess the cost-effectiveness of these agents, we conducted a comprehensive pharmacoeconomic and policy analysis of oral and topical therapies for onychomycosis from a managed care perspective in the United States .

METHODS

A decision analytic model was developed to assess various treatment modalities for onychomycosis. This model structure was developed utilizing available clinical data with the guidance of a panel of practicing dermatologists and onychomycosis experts. The decision analytic model was populated using clinical data derived through a meta-analysis, resource utilization data determined by the expert panel, and resource value data provided by public data sources (see original models in Marchetti 1996, Arikian 1994, and Einarson 1995b). The perspective of this study was a hypothetical managed care organization in the United States. The

timeline for the analysis was 3 years for toenail and 2 years for fingernail. A policy analysis was conducted to project patient-level pharmacoeconomic endpoints for a hypothetical managed care membership population. The treatments included in the evaluation were itraconazole–continuous (Sporanox), itraconazole–pulse (Sporanox), terbinafine (Lamisil), and ciclopirox.

Meta-analysis

This meta-analysis represents an update of a previous meta-analysis (Marchetti 1996).

A comprehensive literature search in both MEDLINE and EMBASE was undertaken to identify all papers published from 1985 through 2001 on the treatment of onychomycosis with itraconazole–pulse, itraconazole–continuous, terbinafine, and ciclopirox. Abstract retrieval was restricted to studies reported in English (or with an English abstract).

Inclusion and exclusion criteria are reported in Table 1. Of all the studies identified in the search, 44 were excluded for various reasons (Table 2). As a result, 40 clinical trials were used in the analysis. Those trials reported data from 3,248 patients.

An attempt was made to use only randomized, double-blind, comparative trials in an effort to minimize bias. Because many of the trials were open-label, however, a limited number of such trials were assessed and subsequently included in the analysis for terbinafine and itraconazole for fingernail and relapse data. Heterogeneity tests were conducted to minimize bias in the results. Two separate investigators carried out data extraction independently, and consensus was reached through discussion.

Meta-analysis was then performed on extracted data to summarize rates across all available literature. Relevant clinical outcomes included success, failure, or relapse. Success was defined as mycological cure, defined as a negative microscopy examination in potassium

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TABLE 1 Criteria for efficacy study identification

Inclusion criteria
· Adult patients
· Onychomycosis or tinea unguium caused by dermatophytes
· Success defined as mycological cure only
· Dosage and treatment lengths within currently suggested ranges
· Success recorded as per protocol

Exclusion criteria
· Onychomycosis caused by yeast or mold*
· Immunocompromised patients
· Patients with concurrent psoriasis of the nails

*Three studies that reported less than 3 percent of the total study population with yeast were included.

TABLE 2   Log of rejected studies (n=44) and reasons for rejections

Of all studies identified in the literature search, 44 were excluded for reasons listed below. As a result, 40 clinical trials were used in the analysis. Those trials reported data from 3,248 patients. Results are presented in subsequent tables.

Reason for rejection	Studies rejected
Could not extract data (5)	Baran 2000, Effendy 1993, Heikkila 1997, Odom 1996, Qadripur 1981
Inappropriate patients (4)	Hanifin 1988, Lee 1996, Nejjam 1995, Velthius 1995
Inappropriate infection/diagnosis (15)	Alpsoy 1996, Bonifaz 1997, Chen 1999, De Doncker 1997, Ellis 1997a, Fiallo 2001, Gontijo 1998, Haneke 1998a, Haneke 1998b, Kim 1995, Matsumoto 1999, Shemer 1999, Tang 2000, Ulbricht 1994, Wong 1995
Not efficacy trial (5)	Andre 1995, Ellis 1997b, Pierard-Franchimont 1995, Piraccini 1996, Schatz 1995
Review only (7)	Dover 1995, Dover 1997, Haneke 1996, Hogan 1995, Odom 1997a, Shear 1995, Van Doorslaer 1996
Duplicate study/results (6)	Brandrup 1997, Brautigam 1996, De Cuyper 1996, De Cuyper 1999, Elewski 1997b, Evans 1999
Inappropriate regimen (2)	Goodfield 2000, Ricketti 2001

hydroxide (KOH) and negative culture. Using an adapted random effects model for meta-analysis, modified for single groups, the overall effectiveness of each therapy was determined separately for onychomycosis of the fingernail and toenail (Einarson 1997). Relapse rate was defined as a recurrence of the infection within 1 month after an initial success. In the absence of relapse rate reported for ciclopirox, a rate of 20.70 percent was used, as reported by a previous meta-analysis (Gupta 2000a). Incidence rates for adverse drug reactions were taken from the package inserts of each drug assessed.

Cost-of-drug analysis

The calculation of drug acquisition cost (DAC) incorporated the determination of drug price (*2001 Red Book*), available package size, administration method and dosage per day. DAC was derived by applying 2001 *Red Book* average wholesale prices (AWP) to the following formula:

$$DAC = (\text{per tablet cost}) \times (\text{total tablets})$$

The cost of Penlac was calculated on the assumption that treatment lasted for 48 weeks (from package insert), using six bottles (3.33 mL each) at $65.56/bottle (Table 3). The assumed

usage was based on the estimations of the panel of expert dermatologists consulted for this study.

Cost-of-regimen analysis

Cost of regimen is a calculation of all direct medical costs for each treatment regimen, including DAC. Direct costs represent the amount expended on medical services. In this analysis, direct costs were segmented into the following categories: drug, routine medical care (including laboratory testing), and adverse events management. Drug cost consisted of the DAC (described above), while routine medical care costs consisted of all the visits, procedures, and tests necessary for treatment and monitoring. Adverse events management costs were calculated as a function of resources consumed in treating the event and the incidence of the event.

Clinical parameters and indirect costs were not included in this calculation. Financial data included public and proprietary sources (i.e., HCFA, NCHS, and UCR fee schedules) (PMIC 1997).

Expected-cost analysis

The cost-of-regimen analysis described above is a necessary step in

economic modeling, but it is somewhat misleading because it does not account for clinical outcomes. Expected-cost analysis addresses this issue by incorporating outcomes into the calculations. In this analysis, the total net cost of each treatment is adjusted to account for the cost of additional therapy when treatment fails or relapse occurs, as determined in the intent-to-treat model. Expected cost represents the product of the probabilities of each outcome and the cost per patient treated.

Disease-free days

Due to the lack of prospectively determined quality-of-life (QoL), data for onychomycosis, disease-free days (DFDs) were used as a proxy for QoL. DFDs constitute the timeframe from clinical success to either relapse or arrival at endpoint of the therapeutic time horizon (i.e., 2 years for fingernail or 3 years for toenail) (Arikian 1994). Expected cost per DFD was calculated by dividing total expected cost of each therapy by total number of DFDs for each treatment.

Cost-effectiveness analysis

The primary cost-effectiveness endpoint was cost per DFD. We cal-

TABLE 3   Cost-of-drug and cost-of-regimen analysis

	Itraconazole–continuous	Itraconazole–pulse	Terbinafine	Ciclopirox
Unit	*Capsule*	*Capsule*	*Tablet*	*Bottle (3.33 mL)*
Toenail				
Pulse days/cycle	NA	7	NA	NA
Dosage/unit	100 mg	100 mg	250 mg	NA
Length of treatment	12 weeks	3 cycles	12 weeks	48 weeks
Units/day	2	4	1	NA
Total units	168	84	84	6
Cost/unit	$7.78	$7.78	$8.35	$65.56
Drug acquisition cost	$1,307	$54	$701	$393
Adverse events	$12	$12	$2	NA
Medical care	$464	$464	$402	$289
Cost of regimen	**$1,783**	**$1,130**	**$1,106**	**$682**
Fingernail				
Pulse days/cycle	NA	7	NA	NA
Dosage/unit	100 mg	100 mg	250 mg	NA
Length of treatment	12 weeks	2 cycles	6 weeks	24 weeks
Units/day	1	4	1	NA
Total units	84	56	42	3
Cost/unit	$7.78	$7.78	$8.35	$65.56
Drug acquisition cost	$654	$436	$351	$197
Adverse events	$3	$3	$2	NA
Medical care	$413	$413	$313	$187
Cost of regimen	**$1,070**	**$852**	**$666**	**$384**

culated the relative cost-effectiveness ratio for each therapy by comparing each drug's cost-effectiveness ratio to the most cost-effective drug.

Policy analysis

The perspective of this analysis was that of the U.S. managed care payer. To facilitate policy-level decision making, we conducted a net economic (budget) impact analysis that detailed population (membership) level implications of each treatment selection. A three-step approach was used for this policy-level analysis. First, the expected cost of treatment per onychomycosis patient was calculated; next, the direct cost (to managed care) of onychomycosis treatment was determined using a *treated-prevalence* approach. *Treated prevalence* was calculated in the following manner:

1) Determine the number of covered lives in the plan; N_L

2) Estimate onychomycosis prevalence in the plan based on published epidemiology data; P_O
3) Determine total patients in the plan that are expected to have onychomycosis at any given time; $(N_L * P_O)$
4) Estimate the percent of members with onychomycosis who typically receive treatment paid by the plan; P_T
5) Determine the total patients treated; $[(N_L * P_O) * P_T]$

Finally, the net budget impact of each drug at different utilization rates was evaluated for the managed care payer at the membership level.

Sensitivity analysis

A sensitivity analysis was performed to test assumptions implicit in the model. Rank order stability analysis (ROSA) (Einarson 1995a), a

univariate break-even analysis, was conducted for key model variables including success rates, drug prices, medical care cost, and length of treatment. Additionally, efficacy rates were varied randomly within the 95 percent confidence interval (as defined by the meta-analysis) based on a truncated normal distribution. Financial values were varied randomly within +/- 15 percent of the estimated cost based on a uniform distribution.

RESULTS
Meta-analysis

Onychomycosis of the fingernail. In general, clinical success rates were higher for fingernail than for toenail onychomycosis (Table 4). As published data were unavailable for ciclopirox in fingernail treatment, the average improvement observed between toenail and fingernail for the other agents was used to estimate ciclopirox efficacy in fingernail. More specifically, a 34.28 percent improvement rate was applied over the toenail efficacy rate of ciclopirox (32.08 percent), which resulted in a 43.07 percent efficacy rate for ciclopirox in fingernail.

The authors' assumption that the efficacy of an oral agent can be used to extrapolate and estimate efficacy of a topical agent on fingernails is based on the belief that treatment of fingernail infections will inherently result in a higher cure rate than toenails, mainly due to the physiology of the infections and not due to the particulars of the type of treatment. In other words, toenail infections are more "stubborn." The investigators have used the relative efficacy for oral agents as a conservative proxy, given that the only other reasonable assumption would be that the efficacy was the same in fingernails as in toes, and this was deemed to be an unfair assumption for Penlac. Furthermore, this is a conservative assumption, because in all likelihood, a topical treatment applied to the hands is less convenient than the toes, potentially

TABLE 4   Summary of success and relapse rates

Drug	Infection site	Patients	Trials	References	Mean (SE)	95% CI limits Lower	Upper
Itraconazole–continuous	Fingernail	61	4	Hay 1987, Hay 1988, Walsoe 1990 (2 groups)	0.926 (0.054)	0.82	1
	Toenail	763	13	Arenas 1991, Arenas 1995, Brautigam 1998, De Backer 1996, Degreef 1999, Havu 1997, Hay 1988, Honeyman 1997, Jones 1996, Korting 1993, Piepponen 1992, Walsoe 1990 (2 groups)	0.645 (0.060)	0.52	0.77
	Relapse	175	7	Arenas 1995, Hay 1987, Hay 1988 (2 groups), Jones 1996, Piepponen 1992, Walsoe 1990	0.263 (0.068)	0.13	0.4
Itraconazole–pulse	Fingernail	84	3	Odom 1997b, Tosti 1996, Wang 1999	0.793 (0.044)	0.71	0.88
	Toenail	692	11	De Doncker 1996 (2 groups), Ginter 1998, Gupta 2000b, Gupta 2001, Havu 1997, Kejda 1999, Ramos-e-Silva 1998, Sigurgeirsson 1999, Tosti 1996, Wang 1999	0.565 (0.044)	0.36	0.77
	Relapse	34	2	De Doncker 1996 (2 groups)	0.176 (0.065)	0.05	0.3
Terbinafine	Fingernail	142	7	Baudraz-Rosselet 1992, Goodfield 1992, Haneke 1995, Torok 1998, Tosti 1996, van der Schroeff 1992, Zaias 1990	0.965 (0.021)	0.93	1
	Toenail	1250	22	Arenas 1995, Baudraz-Rosselet 1992, Billstein 1999, Brautigam 1998, De Backer 1996, Degreef 1999, Faergemann 1995, Goodfield 1992, Gupta 2001, Havu 2000, Honeyman 1997, Kejda 1999, Sigurgeirsson 1999, Smith 2000, Svejgaard 1997 (2 groups), Tausch 1997, Torok 1998, Tosti 1996 (2 groups), van der Schroeff 1992, Watson 1995	0.811 (0.025)	0.76	0.86
	Relapse	285	8	Arenas 1995, Baudraz-Rosselet 1992 (2 groups), Goodfield 1992 (2 groups), Hofmann 1995, Honeyman 1997, van der Schroeff 1992	0.064 (0.014)	0.04	0.09
Ciclopirox	Fingernail	NA	NA		0.431	NA	NA
	Toenail	220	2	Penlac package insert 2001	0.321 (0.035)	0.25	0.39
	Relapse*	NA	NA		0.207	NA	NA

CI = confidence interval; NA = not available
*Incremental average of all drugs (34.28 percent)

making treatment of the fingernails more difficult with topical agents (i.e., lower than expected efficacy). This same disadvantage in treating fingernails would not apply to oral agents.

Overall, terbinafine had the highest success rate (96.5 percent) of the four drugs examined for the primary treatment of onychomycosis of the fingernail, followed by itracona-zole–continuous (92.6 percent), itraconazole–pulse (79.3 percent), and ciclopirox (43.1 percent).

Onychomycosis of the toenail. Terbinafine had the highest success rate (81.1 percent), followed by itraconazole–continuous (64.5 percent), itraconazole–pulse (56.5 percent), and ciclopirox (32.1 percent).

A total of 17 studies presented data from 494 patients for relapse. Terbinafine had the lowest relapse rate (6.42 percent), followed by itraconazole–pulse (17.60 percent), ciclopirox (20.70 percent), and itraconazole–continuous (26.38 percent).

A total of 26 studies presented data from 2,252 patients for adverse drug reactions. As it was deemed more appropriate to use the adverse event rates reported in the package insert

where available, these rates were used for itraconazole–continuous, itraconazole–pulse, and terbinafine (Table 5). No adverse events leading to discontinuation of ciclopirox treatment were reported. As a result, for itraconazole–continuous, the most common reactions were elevated liver enzymes (4.0 percent) and rash (3.0 percent). With terbinafine, the most commonly reported adverse events were rash and visual disturbance (both 0.9 percent).

Cost-of- drug and cost-of-regimen analyses

Table 3 illustrates the dosage, cost per unit, overall DAC, and cost of regimen for all comparators. The DAC for terbinafine in toenails and fingernails was $701 and $351, respectively. Itraconazole–continuous was

TABLE 5   Adverse events leading to temporary or permanent treatment discontinuation

Adverse events	Percent reported
Terbinafine	
Abdominal pain	0.4
Diarrhea	0.6
Dyspepsia	0.4
Headache	0.2
Liver enzyme abnormalities ≥2x upper limit of normal range	0.2
Nausea	0.2
Pruritus	0.2
Rash	0.9
Taste disturbance	0.2
Visual disturbance	0.9
Itraconazole–continuous	
Liver enzyme abnormalities	4.0
Gastrointestinal	4.0
Headache	1.0
Hypertension	2.0
Malaise	1.0
Myalgia	1.0
Orthostatic hypertension	1.0
Rash	3.0
Vasculitis	1.0
Hypertriglyceridemia	3.0
Rash/pruritus	3.0

the highest for toenail ($1,307) and fingernail ($654). Terbinafine demonstrated a regimen cost of $1,106 in toenails and $666 in fingernails, while itraconazole–continuous proved the highest in toenail ($1,783) and fingernail ($1,070). A breakdown of the regimen cost indicates that medical care is a significant contributor of cost to the treatment of both toenails and fingernails across comparators.

Expected-cost analysis

Terbinafine had the lowest overall expected cost ($755) for fingernail infections, followed by ciclopirox ($854), itraconazole–pulse ($1,136) and itraconazole–continuous ($1,395). Terbinafine also had an overall expected cost of $1,574 for toenail infections, closely following ciclopirox ($1,568), and lower than itraconazole–pulse ($1,796), and itraconazole–continuous ($2,566).

Disease-free days

Table 6 summarizes the expected disease-free days (DFDs) for each treatment comparator. In summary, terbinafine treatment yielded the highest number of DFDs (844) for toenail infections followed by itraconazole–continuous (817), itraconazole–pulse (805), and ciclopirox (511). Terbinafine treatment also yielded the highest number of DFDs (622) for fingernail infections, followed by itraconazole–pulse (594), itraconazole–continuous (562), and ciclopirox (452).

Cost-effectiveness analysis

Terbinafine was the most cost-effective alternative, as demonstrated by the relative cost-effectiveness analyses (Table 6). That is, terbinafine had the lowest expected cost per patient while providing a superior success rate and more DFDs to toenail and fingernail patients. Subsequently, terbinafine provided the most favorable average cost per disease-free day ratio ($1.86/DFD) for toenail,

followed by itraconazole–pulse ($2.23/DFD), ciclopirox ($3.07/DFD), and itraconazole–continuous ($3.14/DFD). Terbinafine also provided the most favorable average cost per disease-free day ratio ($1.21/DFD) for fingernail, followed by ciclopirox ($1.89/DFD), itraconazole–pulse ($1.91/DFD) and itraconazole–continuous ($2.48/DFD).

Policy analysis

We utilized data from a hypothetical managed care plan consisting of 1,010,000 covered lives in the budget impact matrix. Of this population, it was estimated that 4 percent (n=40,400) suffer from onychomycosis and are potential candidates for treatment therapy. A conservative assumption of 10 percent of patients receiving therapy was made for the analysis.

According to epidemiologic data, about 80 percent of onychomycosis infections affect the toenails, and 20 percent affect the fingernails. Although patients often present with both toenail and fingernail infection, to be conservative, we have assumed mutual exclusivity. This translates to 3,232 patients being treated for toenail infections and 808 patients treated for fingernail infections in our representative plan membership population. Using these data, we calculated annual cost per patient and total annual budget for onychomycosis (Figure 1). Additionally, increasing utilization of terbinafine from 0 percent to 100 percent for the treated population is expected to yield total annual savings of $535,165. In other words, if the plan utilized terbinafine 0 percent of the time, it would incur a total annual treatment cost of $2,529,849 or $0.21 per member per month (PMPM). Switching entirely to terbinafine (100 percent terbinafine utilization) from all other antifungal utilization would reduce total annual treatment cost to $1,994,684 or $0.16 PMPM (Figure 2). Results of this analysis suggest that

TABLE 6 Calculation of total disease-free days and cost-effectiveness analysis of onychomycosis therapy, expressed as cost per disease-free day

	Itraconazole–continuous	Itraconazole–pulse	Terbinafine	Ciclopirox
Toenail				
Disease-free days (DFDs)	817	805	844	511
Cost/DFD	$3.14	$2.23	$1.86	$3.07
Relative cost-effectiveness compared with terbinafine	1.68	1.20	1.00	1.65
Fingernail				
DFDs	562	594	622	452
Cost/DFD	$2.48	$1.91	$1.21	$1.89
Relative cost-effectiveness compared with terbinafine	2.04	1.58	1.00	1.59

terbinafine is the least costly therapy for onychomycosis from a managed care perspective.

Sensitivity analysis

ROSA demonstrated stability across all scenarios. For example, for terbinafine to be displaced as having the lowest expected cost for the treatment of toenail onychomycosis, its total DAC would have to exceed $1,102.70 or be below $686.09. Conversely, the total DAC for itraconazole–continuous would have to decrease from $1,307.04 to $649.06 for the results of this analysis to change. The DAC for itraconazole–pulse would have to decrease from $653.52 to $450.21. Results are more sensitive to the efficacy of terbinafine as compared with the efficacy of the other agents because its reduced cost of failure causes a lower expected cost.

DISCUSSION

In treating onychomycosis, this study clearly confirms previous reports that demonstrate terbinafine to be economically superior to the oral and topical therapies evaluated in this analysis. There are studies that highlight the cost-effectiveness of itraconazole vs. "other" therapies. Nevertheless, the investigators know of no publications that claim that itra-

conazole is more cost-effective than terbinafine. Itraconazole has been shown to be more cost-effective than agents such as griseofulvin and even fluconazole, due to their lower reported cure rates. Yet this is not necessarily the case with terbinafine, mainly because costs are relatively similar while the cure rates associated with terbinafine are reportedly higher (Darkes 2003, Jansen 2001).

The fungicidal property of terbinafine has produced clinical advantages that are reflected in higher success rates and lower relapse rates for both fingernail and toenail infections.

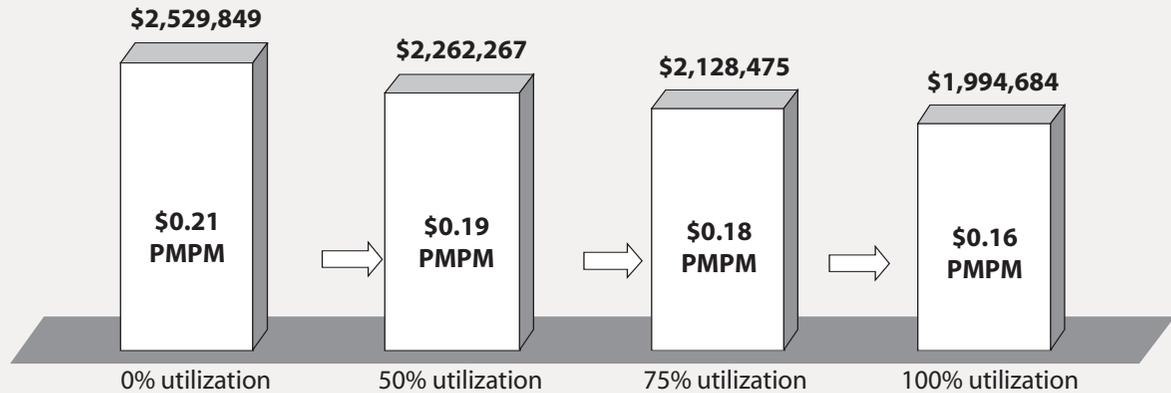Terbinafine is primarily fungicidal in its mode of action, whereas itra-

FIGURE 1 Budget impact analysis
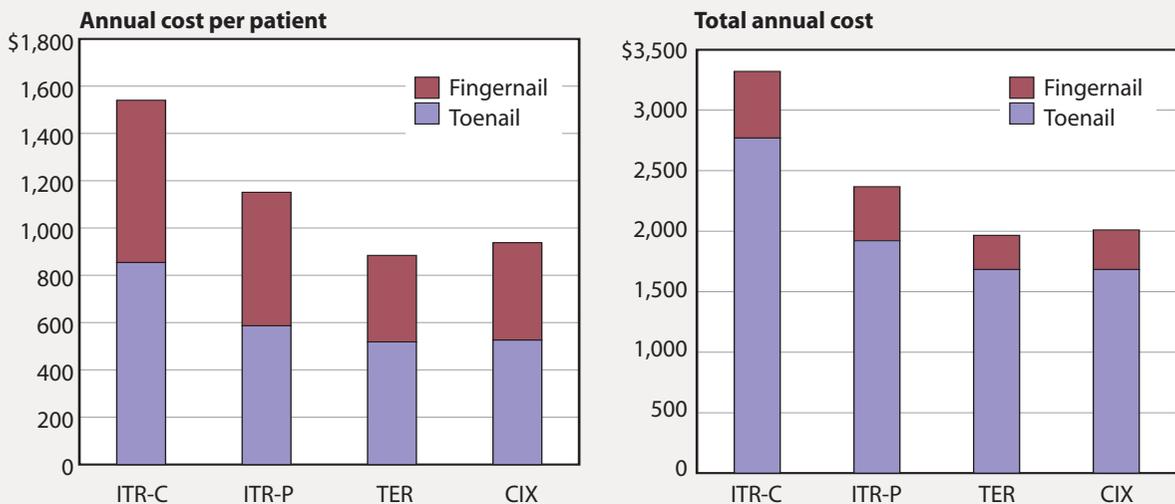
ITR-C = itraconazole–continuous, ITR-P = itraconazole–pulse, TER = terbinafine, CIX = ciclopirox

FIGURE 2 Budget impact model for terbinafine utilization

Total onychomycosis treatment cost (1,010,000 covered lives)

conazole is primarily fungistatic. Terbinafine provides superior long-term mycological and clinical efficacy and lower rates of mycological and clinical relapse compared with intermittent itraconazole (Sigurgeirsson 2002).

Aside from the economic advantage to the payer, there are advantages to the patient. The reduced length of treatment, as compared with newer drugs such as ciclopirox, encourages higher rates of compliance with treatment regimens that yield higher efficacy rates. The fewer relapses associated with terbinafine in comparison with itraconazole–continuous, itraconazole–pulse, and ciclopirox allow the patient more disease-free days, which lead to a presumed improvement in patient quality of life.

The validity of the outcomes of this analysis depends on the quality of the inputs. We used the best available evidence to estimate success rates for these drugs, using randomized controlled trials where available. In all cases, results were verified with an expert panel of practicing dermatologists. The meta-analysis used standard techniques, including use of two independent evaluators and the more conservative random effects model.

Additionally, differences in real-world settings can affect results of the analysis. For example misdiagnosis can result in prescribing for inappropriate patients, as well as underdiagnosis that results in patients not being treated. Though these circumstances can lead to variations in cost results, they have not been considered in this analysis due to lack of data.

Sensitivity analysis indicates that calculations were robust against perturbations in assumptions and estimations regarding model inputs. For all plausible values, terbinafine remained the treatment alternative demonstrating the lowest expected cost for the treatment of onychomycosis. The specifics of other health care settings should be examined, however.

CONCLUSION

This study confirms the results of previous pharmacoeconomic analyses of onychomycosis, that terbinafine is the most cost-effective choice for treating onychomycosis. For both fingernail and toenail infections, terbinafine dominated all treatment alternatives evaluated in the decision analytic model. Pharmacoeconomic dominance provides pressing evidence for adopting terbinafine as the drug of choice for the treatment of onychomycosis.

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REFERENCES

2001 Red Book. Montvale, N.J.: Medical Economics Co. Inc.; 2001.

Alpsoy E, Yilmaz E, Basaran E. Intermittent therapy with terbinafine for dermatophyte toe-onychomycosis: a new approach. *J Dermatol.* 1996;23:259–262.

Andre J, De Doncker P, Laporte M, et al. Onychomycosis caused by *Microsporum canis*: treatment with itraconazole. *J Am Acad Dermatol.* 1995;32:1052–1053.

Arenas R, Fernandez G, Dominguez L. Onychomycosis treated with itraconazole or griseofulvin alone with and without a topical antimycotic or keratolytic agent. *Int J Dermatol.* 1991;30:586–589.

Arenas R, Dominguez-Cherit J, Fernandez LM. Open randomized comparison of itraconazole versus terbinafine in onychomycosis. *Int J Dermatol.* 1995;34:138–143.

Arikian SR, Einarson TR, Kobelt-Nguyen G, Schubert F. A multinational pharmacoeconomic analysis of oral therapies for onychomycosis. The

Onychomycosis Study Group. *Br J Dermatol*. 1994;130(suppl 43):35-44.

Baran R, Feuilhade M, Combernale P, et al. A randomized trial of amorolfine 5% solution nail lacquer combined with oral terbinafine compared with terbinafine alone in the treatment of dermatophytic toenail onychomycoses affecting the matrix region. *Br J Dermatol*. 2000 Jun;142: 1177–1183.

Baudraz-Rosselet F, Rakosi T, Wili PB, Kenzelmann R. Treatment of onychomycosis with terbinafine. *Br J Dermatol*. 1992;126(suppl 39):40–46.

Billstein S, Kianifard F, Justice A. Terbinafine vs. placebo for onychomycosis in black patients. *Int J Dermatol*. 1999;38:377–379.

Bonifaz A, Carrasco-Gerard E, Saul A. Itraconazole in onychomycosis: intermittent dose schedule. *Int J Dermatol*. 1997;36:70–72.

Boyko WL, Doyle JJ, Ryu S, Gause D. Onychomycosis and its impact on secondary infection development in the diabetic population. Presented at: 4th Annual International Meeting of the International Society for Pharmacoeconomics and Outcomes Research (ISPOR); May 23-26, 1999.

Brandrup F, Larsen PO. Long-term follow-up of toe-nail onychomycosis treated with terbinafine [letter]. *Acta Derm Venereol*. 1997;77:238.

Brautigam M. Terbinafine versus itraconazole: a controlled clinical comparison in onychomycosis of the toenails. *J Am Acad Dermatol*. 1998;38(5 Pt 3): S53–S56.

Brautigam M, Nolting S, Schopf RE, Weidinger G. German randomized double-blind multicentre comparison of terbinafine and itraconazole for the treatment of toenail tinea infection. *Br J Dermatol*. 1996;134(Suppl 46):18-21.

Chen J, Liao W, Wen H, Wu J, Yao Z. A comparison among four regimens of itraconazole treatment in onychomycosis. *Mycoses*. 1999;42:93–96.

Darkes MJ, Scott LJ, Goa KL. Terbinafine: a review of its use in onychomycosis in adults. *Am J Clin Dermatol*. 2003;4:39-65.

Davis R, Balfour JA. Terbinafine. A pharmacoeconomic evaluation of its use in superficial fungal infections. *Pharmacoeconomics* (New Zealand). 1995;8:253–269.

De Backer M, De Keyser P, De Vroey C, Lesaffre E. A 12-week treatment for dermatophyte toe onychomycosis: terbinafine 250 mg/day vs. itraconazole 200 mg/day—a double-blind comparative trial. *Br J Dermatol*. 1996;134(suppl 46):16–17.

De Cuyper C. Long-term evaluation of terbinafine 250 and 500 mg daily in a 16-week oral treatment for toenail onychomycosis [letter]. *Br J Dermatol*. 1996;135:156–157.

De Cuyper C, Hindryckx PHFB. Long-term outcomes in the treatment of toenail onychomycosis. *Br J Dermatol*. 1999;141(suppl 56):15-20.

De Doncker P, Decroix J, Pierard GE, et al. Antifungal pulse therapy for onychomycosis. A pharmacokinetic and pharmacodynamic investigation of monthly cycles of 1-week pulse therapy with itraconazole. *Arch Dermatol*. 1996;132:34-41.

De Doncker PR, Scher RK, Baran RL, et al. Itraconazole therapy is effective for pedal onychomycosis caused by some nondermatophyte molds and in mixed infection with dermatophytes and molds: a multicenter study with 36 patients. *J Am Acad Dermatol*. 1997;36(2 Pt 1):173–177.

Degreef H, del Palacio A, Mygind S, et al. Randomized double-blind comparison of short-term itraconazole and terbinafine therapy for toenail onychomycosis. *Acta Derm Venereol*. 1999;79:221–223.

Dover JS, Arndt KA. Dermatology. Three new systemic fungicidal drugs have been developed in the treatment of tinea unguium. *JAMA*. 1995; 273:1668–1670.

Dover JS, Arndt KA. Dermatology. Itraconazole and terbinafine for fungal infections of the nails. *JAMA*. 1997;277:1848–1850.

Drake L. Quality of life issues for patients with fungal nail infections. *AIDS Patient Care*. 1995;9(suppl 1):S15–S17.

Effendy I, Kolczak H, Ossowski B, Hohler T. [Topical therapy of onychomycoses with 8% ciclopirox lacquer. An open, non-comparative study]. *Fortschr Med*. 1993;111:205–208.

Einarson TR, Arikian SR, Doyle JJ. Rank-order stability analysis (ROSA): Testing pharmacoeconomic data. *Med Decis Making*. 1995a;15:367–372.

Einarson TR, Arikian SR, Shear NH. Cost-effectiveness analysis for onychomycosis therapy in Canada from a government perspective. *Br J Dermatol*. 1994;130(suppl. 43):32–34.

Einarson TR, Arikian SR, Shear NH. Pharmacoeconomic analysis of oral treatments for onychomycosis: A Canadian study. *J Res Pharm Economics*. 1995b;6:3-22.

Einarson TR. Pharmacoeconomic applications of meta-analysis for single groups using antifungal onychomycosis lacquers as an example. *Clin Ther*. 1997;19:559–569.

Elewski BE, Charif MA. Prevalence of onychomycosis in patients attending a dermatology clinic in northeastern Ohio for other conditions. *Arch Dermatol*. 1997a;133:1172–1173.

Elewski BE, Scher RK, Aly R, et al. Double-blind, randomized comparison of itraconazole capsules vs. placebo in the treatment of toenail onychomycosis. *Cutis*. 1997b;59:217–220.

Ellis DH, Marley JE, Watson AB, Williams TG. Significance of nondermatophyte moulds and yeasts in onychomycosis. *Dermatology*. 1997a;194 (suppl 1):40–42.

Ellis DH, Watson AB, Marley JE, Williams TG. Non-dermatophytes in onychomycosis of the toenails. *Br J Dermatol*. 1997b;136:490–493.

Evans EGV, Sigurgeirsson B. Double blind, randomized study of continuous terbinafine compared with intermittent itraconazole in treatment of toenail onychomycosis. *BMJ*. 1999; 318:1031–1035.

Faergemann J, Anderson C, Hersle K, et al. Double-blind, parallel-group comparison of terbinafine and griseofulvin in the treatment of toenail onychomycosis. *J Am Acad Dermatol*. 1995;32(5 Pt 1):750–753.

Fiallo P, Cardo PP. Age as limiting factor of the efficacy of itraconazole for treatment of onychomycosis. *Mycoses*. 2001;44:191–194.

Ginter G, De Doncker P. An intermittent itraconazole 1-week dosing regimen for the treatment of toenail onychomycosis in dermatological practice. *Mycoses*. 1998;41:235–238.

Goldfarb NJ, Sulzberger MB. Experiences in one hundred thirty-seven patients treated with oral griseofulvin. *Arch Dermatol*. 1960;81:859–862.

Gontijo B, Zaitz C, Bartelle C, Azulay DR, Campbell I, Cestar S. Avaliacao do ciclopirox no tratamento das onicomicoses. *An Bras Dermatol*. 1998;73:395–401.

Goodfield MJD, Andrew L, Evans EGV. Short term treatment of dermatophyte onychomycosis with terbinafine. *BMJ*. 1992;304:1151–1154.

Goodfield MJD, Evans EGV. Combined treatment with surgery and short duration oral antifungal therapy in patients with limited dermatophyte toenail infection. *J Dermatolog Treat*. 2000;11:259–262.

Gupta AK. Pharmacoeconomic analysis of oral antifungal therapies used to treat dermatophyte onychomycosis of the

toenails. A US analysis. *Pharmacoeconomics.* 1998;13: 243–256.

Gupta AK. Pharmacoeconomic analysis of ciclopirox nail lacquer solution 8% and the new oral antifungal agents used to treat dermatophyte toe onychomycosis in the United States. *J Am Acad Dermatol.* 2000a;43:S70-S80.

Gupta AK, Konnikov N, Lynde CW. Single-blind, randomized, prospective study on terbinafine and itraconazole for treatment of dermatophyte toenail onychomycosis in the elderly. *J Am Acad Dermatol.* 2001;44:479–484.

Gupta AK, Maddin S, Arlette J, Giroux JM, Shear NH. Itraconazole pulse therapy is effective in dermatophyte onychomycosis of the toenail: a double-blind placebo-controlled study. *J Dermatolog Treat.* 2000b;11:33–37.

Haneke E, Abeck D, Ring J. Safety and efficacy of intermittent therapy with itraconazole in finger- and toenail onychomycosis: a multicentre trial. *Mycoses.* 1998a;41:521–527.

Haneke E, Delescluse J, Plinck EPB, Hay RJ. The use of itraconazole in onychomycosis. *Eur J Dermatol.* 1996:6:7–10.

Haneke E, Tajerbashi M, De Doncker P, Heremans A. Itraconazole in the treatment of onychomycosis: a double-blind comparison with miconazole. *Dermatology.* 1998b;196:323–329.

Haneke E, Tausch I, Brautigam M, Weidinger G, Welzel D. Short-duration treatment of fingernail dermatophytosis: a randomized, double-blind study with terbinafine and griseofulvin. LAGOS III Study Group. *J Am Acad Dermatol.* 1995;32:72–77.

Hanifin JM, Tofte SJ. Itraconazole therapy for recalcitrant dermatophyte infections. *J Am Acad Dermatol.* 1988;18(5 Pt 1):1077–1080.

Havu V, Brandt H, Heikkila H, et al. A double-blind, randomized study comparing itraconazole pulse therapy with continuous dosing for the treatment of toe-nail onychomycosis. *Br J Dermatol.* 1997;136:230–234.

Havu V, Heikkila H, Kuokkanen K, et al. A double-blind, randomized study to compare the efficacy and safety of terbinafine (Lamisil) with fluconazole (Diflucan) in the treatment of onychomycosis. *Br J Dermatol.* 2000;142:97–102.

Hay RJ, Clayton YM. Treatment of chronic dermatophytosis and chronic oral candidosis with itraconazole. *Rev Infect Dis.* 1987;9(suppl 1):S114–S118.

Hay RJ, Clayton YM, Moore MK, Midgely G. An evaluation of itraconazole in the management of onychomycosis. *Br J Dermatol.* 1988;119:359–366.

Heikkila H, Stubb S. Long-term results of patients with onychomycosis treated with itraconazole. *Acta Derm Venereol.* 1997;77:70–71.

Hofmann H, Brautigam M, Weidinger G, Zaun H. Treatment of toenail onychomycosis. A randomized, double-blind study with terbinafine and griseofulvin. LAGOS II Study Group. *Arch Dermatol.* 1995;131:919–922.

Hogan DJ. Short-duration treatment of fingernail dermatophytosis: a randomized, double-blind study with terbinafine and griseofulvin. *J Am Acad Dermatol.* 1995;33:541–542.

Honeyman JF, Talarico F, Aruda LHF, et al. Iteraconazole versus terbinafine (Lamisil): which is better for the treatment of onychomycosis? *J Eur Acad Dermatol Venereol.* 1997;9:215–221.

Jansen R, Redekop WK, Rutten FF. Cost effectiveness of continuous terbinafine compared with intermittent itraconazole in the treatment of dermatophyte toenail onychomycosis: an analysis of based on results from the L.I.ON. study. Lamisil versus Itraconazole in Onychomycosis. *Pharmacoeconomics.* 2001;19:401–410.

Joish VN, Armstrong EP. Which antifungal agent for onychomycosis? A pharmacoeconomic analysis. *Pharmacoeconomics.* 2001; 19(10): 983-1002.

Jones HE, Zaias N. Double-blind, randomized comparison of itraconazole capsules and placebo in onychomycosis of toenail. *Int J Dermatol.* 1996;35:589–590.

Kejda J. Itraconazole pulse therapy vs continuous terbinafine dosing for toenail onychomycosis. *Postgrad Med.* 1999 Jul;Spec No:12–15.

Kim JA, Ahn KJ, Kim JM, Youn JI. Efficacy and tolerability of itraconazole in patients with fingernail onychomycosis: A 6-week pilot study. *Curr Ther Res.* 1995;56:1066–1075.

Korting HC, Schafer-Korting M, Zienicke H, Georgii A, Ollert MW. Treatment of tinea unguium with medium and high doses of ultramicrosize griseofulvin compared with that with itraconazole. *Antimicrob Agents Chemother.* 1993;37:2064–2068.

Lee KH, Kim YS, Kim MS, Chung HS, Park K. Study of the efficacy and tolerability of oral terbinafine in the treatment of onychomycosis in renal transplant patients. *Transplant Proc.* 1996;28:1488–1489.

Levy LA. Epidemiology of onychomycosis in special-risk populations. *J Am Podiatr Med Assoc.* 1997;87:546–550.

Ling MR, Swinyer LJ, Jarratt MT, et al. Once-weekly fluconazole (450 mg) for 4, 6 or 9 months of treatment for subungual onychomycosis of the toenail. *J Am Acad Dermatol.* 1998;38(6 Pt 2):S95–S102.

Lubeck DP, Patrick DL, McNulty P, Fifer SK, Birnbaum J. Quality of life of persons with onychomycosis. *Qual Life Res.* 1993;2:341–348.

Marchetti A, Piech CT, McGhan WF, Neugut AI, Smith BT. Pharmacoeconomic analysis of oral therapies for onychomycosis: A US model. *Clin Ther.* 1996;18:757–777.

Matsumoto T, Tanuma H, Nishiyama S. Clinical and pharmacokinetic investigations of oral intraconazole in the treatment of onychomycosis. *Mycoses.* 1999;42:79-91.

Nejjam F, Zagula M, Cabiac MD, Guessous N, Humbert H, Lakhdar H. Pilot study of terbinafine in children suffering from tinea capitis: evaluation of efficacy, safety and pharmacokinetics. *Br J Dermatol.* 1995;132:98–105.

Odom R, Daniel CR, Aly R. A double-blind, randomized comparison of itraconazole capsules and placebo in the treatment of onychomycosis of the toenail. *J Am Acad Dermatol.* 1996;35:110–111.

Odom RB. Update on topical therapy for superficial fungal infections: focus on butenafine. *J Am Acad Dermatol.* 1997a;36(2 Pt 1):S1–S2.

Odom RB, Aly R, Scher RK, et al. A multicenter, placebo-controlled, double-blind study of intermittent therapy with itraconazole for the treatment of onychomycosis of the fingernail. *J Am Acad Dermatol.* 1997b;36(2 Pt 1):231–235.

Penlac [package insert]. Berwyn, Pa.: Dermik Laboratories, Inc. (Aventis Pharma); 2001.

Physician Fees: A Comprehensive Guide for Fee Schedule Review and Management. Los Angeles: PMIC; 1997.

Piepponen T, Blomqvist K, Brandt H, et al. Efficacy and safety of itraconazole in the long-term treatment of onychomycosis. *J Antimicrob Chemother.* 1992;29:195–205.

Pierard-Franchimont G, De Doncker P, Van de Velde V, Jacqmin P, Arrese JE, Pierard GE. Paradoxical response to itraconazole treatment in a patient with onychomycosis caused by *Microsporum gypseum. Ann Soc Belg Med Trop.* 1995;75:211–217.

Piraccini BM, Morelli R, Stinchi C, Tosti A. Proximal subungual onychomycosis due to *Microsporum canis*. *Br J Dermatol*. 1996;134:175–177.

Qadripur SA, Horn G, Hohler T. [On the local efficacy of ciclopiroxolamine in onychomycoses]. *Arzneimittelforschung*. 1981;31:1369–1372.

Radentz WH. Opportunistic fungal infections in immunocompromised hosts. *J Am Acad Dermatol*. 1989; 20: 989–1003.

Ramos-e-Silva M, Marques SA, Gontijo B, Zaitz C, Campbell I, Veloso ST. Efficacy and safety of itraconazole pulse therapy: Brazilian multicentric study on toenail onychomycosis caused by dermatophytes. *J Eur Acad Dermatol Venereol*. 1998;11:109–116.

Ricketti JC. Terbinafine/miconazole nitrate 2% tincture compound for the treatment of onychomycosis. *Foot*. 2001;11:21–23.

Sais G, Jucgla A, Peyri J. Prevalence of dermatophyte onychomycosis in Spain: a cross-sectional study. *Br J Dermatol*. 1995;132:758–761.

Schatz F, Brautigam M, Dobrowolski E, et al. Nail incorporation kinetics of terbinafine in onychomycosis patients. *Clin Exp Dermatol*. 1995;20: 377–383.

Schein JR, Gause D, Stier DM, Lubeck DP, Bates MM, Fisk R. Onychomycosis. Baseline results of an observational study. *J Am Podiatr Med Assoc*. 1997;87:512–519.

Scher RK, Breneman D, Rich P, et al. Once-weekly fluconazole (150, 300, or 450 mg) in the treatment of distal subungual onychomycosis of the toenail. *J Am Acad Dermatol*. 1998;38(6 Pt 2):S77–S86.

Shear NH, Gupta AK. Terbinafine for the treatment of pedal onychomycosis. A foot closer to the promised land of cured nails? *Arch Dermatol*. 1995;131:937–942.

Shemer A, Nathansohn N, Kaplan B, Gilat D, Newman N, Trau H. Open randomized comparison of different itraconazole regimens for the treatment of onychomycosis. *J Dermatol Treatment*. 1999;10:245–249.

Sigurgeirsson B, Billstein S, Rantanen T, et al. L.I.ON. Study: efficacy and tolerability of continuous terbinafine (Lamisil) compared to intermittent itraconazole in the treatment of toenail onychomycosis. Lamisil vs. Itraconazole in Onychomycosis. *Br J Dermatol*. 1999;141(suppl 56):5–14.

Smith E, Stein L, Fivenson D, Atillasoy ES. The safety of terbinafine in patients over the age of 60 years: a multi-center trial in onychomycosis of the feet. *Int J Dermatol*. 2000;39:859–864.

Sporanox [package insert]. Titusville, N.J.: Janssen Pharmaceutica Products, LP; 2001.

Stier DM, Henke C, Schein J, Doyle J, Schonfeld WH, Broering J. Cost of treatment for onychomycosis: Data from a 9-month observational study. *Pharmacoeconomics*. 2001; 19: 267–279.

Summerbell RC, Kane J, Krajden S. Onychomycosis, tinea pedis and tinea manuum caused by non-dermatophytic filamentous fungi. *Mycoses*. 1989;32:609–619.

Svejgaard EL, Brandrup F, Kragballe K, et al. Oral terbinafine in toenail dermatophytosis. A double-blind, placebo-controlled multicenter study with 12 months' follow-up. *Acta Derm Venereol*. 1997;77:66–69.

Tang WYM, Chong LY, Leung CY, Ho HHF, Wong TW. Intermittent pulse therapy with itraconazole for onychomycosis. Experience in Hong Kong Chinese. *Mycoses*. 2000; 43:35–39.

Tausch I, Brautigam M, Weidinger G, Jones TC. Evaluation of 6 weeks treatment of terbinafine in tinea unguium in a double-blind trial comparing 6 and 12 weeks therapy. The Lagos V Study Group. *Br J Dermatol*. 1997;136:737–742.

Tom CM, Kane MP. Management of toenail onychomycosis. *Am J Health Syst Pharm*. 1999;56:865–871.

Torok I, Simon G, Dobozy A, et al. Long-term post-treatment follow-up of onychomycosis treated with terbinafine: a multicentre trial. *Mycoses*. 1998;41:63–65.

Tosti A, Piraccini BM, Stinchi C, Venturo N, Bardazzi F, Colombo MD. Treatment of dermatophyte nail infections: an open randomized study comparing intermittent terbinafine therapy with continuous terbinafine treatment and intermittent itraconazole therapy. *J Am Acad Dermatol*. 1996;34:595–600.

Ulbricht H, Worz K. [Therapy with ciclopirox lacquer of onychomycoses caused by molds]. *Mycoses*. 1994;37(suppl 1):97-100.

van der Schroeff JG, Cirkel PK, Crijns MB, et al. A randomized treatment duration-finding study of terbinafine in onychomycosis. *Br J Dermatol*. 1992;126(suppl 39):36–39.

Van Doorslaer EK, Tormans G, Gupta AK, et al. Economic evaluation of antifungal agents in the treatment of toenail onychomycosis in Germany. *Dermatology*. 1996;193:239–244.

Velthuis PJ, Nijenhuis M. Treatment of onychomycosis with terbinafine in patients with Down's syndrome. *Br J Dermatol*. 1995;133:144–146.

Walsoe I, Stangerup M, Svejgaard E. Itraconazole in onychomycosis. Open and double-blind studies. *Acta Derm Venereol*. 1990;70:137–140.

Wang DL, Wang AP, Li RY, Wang R. Therapeutic efficacy and safety of one-week intermittent therapy with itraconazole for onychomycosis in a Chinese patient population. *Dermatology*. 1999;199:47–49.

Watson A, Marley J, Ellis D, Williams T. Terbinafine in onychomycosis of the toenail: a novel treatment protocol. *J Am Acad Dermatol*. 1995;33:775–779.

Wong CK, Cho YL. Very short duration therapy with oral terbinafine for fingernail onychomycosis. *Br J Dermatol*. 1995;133:329–331.

Zaias N. Management of onychomycosis with oral terbinafine. *J Am Acad Dermatol*. 1990;23:810–812.